

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 02: Cancer

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine (formerly the Institute of Medicine) and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 5600 Fishers Lane Rockville, MD 20857, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 24,500 leads about potential topics has resulted in identification and tracking of about 2,400 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 750 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 195 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest (COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs.

No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists 38 topics for which (1) preliminary data from a trial intended to support regulatory approval for drugs (i.e., phase III data for most drugs and phase II data for accelerated, fast-track, or orphan drugs), phase II or III data for devices or procedures, or data from pivotal studies were available; (2) information was compiled and sent for expert comment before November 6, 2015, in this priority area; *and* (3) we received six to eight sets of comments from experts between January 1, 2015, and November 6, 2015. (In this priority area, 254 topics were being tracked in the system as of November 6, 2015). Please note that some of the comments received on some interventions predated their approvals by the U.S. Food and Drug Administration (FDA). For this report, we aggregated related topics for summary and discussion (i.e., by drug class and disease) and they are organized alphabetically, first by disease state and then by intervention. We present 15 summaries on 22 topics (indicated in the table by an asterisk) that emerged as having high-impact potential on the basis of expert comments and assessment of potential impact.

Priority Area 02: Cancer

Topics	High-Impact Potential
1. Afatinib (Gilotrif) for treatment of advanced head and neck cancer	No high-impact potential at this time
2. Anamorelin for treatment of cancer-related cachexia/anorexia	No high-impact potential at this time
3. * Blinatumomab (Blinicyto) for treatment of acute lymphoblastic leukemia	Lower end of the high-impact-potential range
4. Cabozantinib (Cometriq) for treatment of renal cell carcinoma	No high-impact potential; archived November 2015 on basis of experts’ comments
5. Capsule endoscopy (PillCam Colon 2) for colorectal cancer screening	No high-impact potential; archived September 2015 on basis of experts’ comments
6. * Crizotinib (Xalkori) for treatment of <i>ROS1</i> -positive nonsmall cell lung cancer	Lower end of the high-impact-potential range
7. * Daratumumab (Darzalex) for treatment of multiple myeloma	Moderately high
8. Denosumab (Xgeva) for treatment of refractory hypercalcemia of malignancy	No further potential for high impact; archived November 2015 on basis of being broadly diffused
9. * Dinutuximab (Unituxin) for treatment of neuroblastoma	Lower end of the high-impact-potential range
10. * Elotuzumab (Empliciti) for treatment of multiple myeloma	Moderately high

Topics	High-Impact Potential
11. High-intensity focused ultrasound (Ablatherm system) for treatment of localized prostate cancer	No high-impact potential; archived September 2015 on basis of experts' comments
12. High-intensity focused ultrasound (Sonablate system) for treatment of localized prostate cancer	No high-impact potential; archived September 2015 on basis of experts' comments
13. * Ibrutinib (Imbruvica) for treatment of chronic lymphocytic leukemia	High
14. Ibrutinib (Imbruvica) for treatment of mantle cell lymphoma	Prior high-impact topic; archived November 2015; tracked in system 2 years after FDA approval
15. * Ibrutinib (Imbruvica) for treatment of Waldenström's macroglobulinemia	High
16. * Idelalisib (Zydelig) for treatment of chronic or small lymphocytic leukemia	High
17. * Idelalisib (Zydelig) for treatment of indolent non-Hodgkin's lymphoma	High
18. Lenvatinib (Lenvima) for treatment of differentiated thyroid cancer	Prior high-impact topic (June 2015); tracked for 2 years after FDA approval and no longer meets horizon scanning criteria for tracking; archived November 2015
19. * Nivolumab (Opdivo) for treatment of advanced renal cell carcinoma	Lower end of the high-impact-potential range
20. * Nivolumab (Opdivo) for treatment of advanced melanoma	Moderately high
21. * Nivolumab (Opdivo) for treatment of nonsmall cell lung cancer	High
22. Obinutuzumab (Gazyva) for treatment of indolent non-Hodgkin's lymphoma	No high-impact potential; archived November 2015 on basis of experts comments
23. Off-label vemurafenib for treatment of hairy cell leukemia	No high-impact potential; archived November 2015 on basis of experts comments
24. * Osimertinib (Tagrisso) for treatment of nonsmall cell lung cancer	Moderately high
25. Ovarian tissue cryopreservation for fertility preservation in females undergoing gonadotoxic cancer therapy	Prior high-impact topic (June 2015); archived November 2015 on basis of lack of diffusion
26. * Palbociclib (Ibrance) for treatment of estrogen receptor-positive breast cancer	Moderately high
27. * Pembrolizumab (Keytruda) for treatment of advanced melanoma	Moderately high
28. * Pembrolizumab (Keytruda) for treatment of nonsmall cell lung cancer	High
29. * Ramucirumab (Cyramza) for treatment of gastric cancer	Lower end of the high-impact-potential range
30. Ramucirumab (Cyramza) for treatment of metastatic colorectal cancer	No high-impact potential; archived November 2015 on basis of experts' comments
31. * Rociletinib for treatment of nonsmall cell lung cancer	Moderately high
32. * Ruxolitinib (Jakafi) for treatment of polycythemia vera	Lower end of the high-impact-potential range
33. * Siltuximab (Sylvant) for treatment of multicentric Castleman's disease	Lower end of the high-impact-potential range
34. Sorafenib (Nexavar) for treatment of differentiated thyroid cancer	Prior high-impact topic (June 2015); archived November 2015
35. * Stool DNA molecular test (Cologuard) for colorectal cancer screening	Lower end of the high-impact-potential range
36. * Talimogene laherparepvec (Imlygic) for treatment of advanced melanoma	Lower end of the high-impact-potential range
37. Trifluridine tipiracil hydrochloride (TAS-102; Lonsurf) for treatment refractory metastatic colorectal cancer	No high-impact potential; archived November 2015 on basis of experts' comments
38. Urocidin for treatment of nonmuscle-invasive bladder cancer	No high-impact potential; archived August 2015 on basis of experts' comments

Discussion

Prior Potential High-Impact Topics Archived

The following four interventions were deemed to have high-impact potential in previous reports but have been archived because they no longer meet criteria for tracking in the AHRQ Healthcare Horizon Scanning System. These interventions have either timed out (being 2 years past FDA approval), fall within the same drug class as an archived drug that is diffusing broadly and fulfilling the unmet need, or the intervention has not diffused.

- **Ibrutinib (Imbruvica) for treatment of mantle cell lymphoma:** Patients with mantle cell lymphoma (MCL) had few options when disease progressed after initial chemotherapy. Median overall survival has been between 5 and 7 years. Ibrutinib is a small-molecule kinase inhibitor with activity against Bruton's tyrosine kinase (Btk). Btk is essential for transduction of the B-cell receptor (BCR) signaling pathway, and many B-cell malignancies (including MCL) depend on BCR signaling for survival; therefore, its inhibition may benefit patients with MCL. FDA approved ibrutinib for treating MCL in November 2013, and the topic was included as a topic with high potential impact in four prior Potential High Impact Reports. The drug has been diffusing for more than 2 years and no longer meets criteria for tracking. We archived the topic in November 2015 in the horizon scanning system.
- **Lenvatinib (Lenvima®) and sorafenib (Nexavar®) for treatment of differentiated thyroid cancer:** Sorafenib and lenvatinib are multiple kinase inhibitors that target the MAP kinase pathway to inhibit tumor cell proliferation and angiogenesis. Both are oral medications administered daily. Although they do not provide a cure, lenvatinib and sorafenib are capable of treating and stabilizing radioactive iodine–refractory thyroid cancer. FDA approved sorafenib in November 2013 and the drug was deemed by expert comments to have potential for high impact; it has been included in previous Potential High Impact Intervention reports since December 2013. The drug has been diffusing for more than 2 years, no longer meets criteria for tracking, and was archived in November 2015 in the horizon scanning system. Lenvatinib was FDA approved in February 2015, and as a drug in the same class has been diffusing. It was also archived in November because of its similarity to sorafenib.
- **Ovarian tissue cryopreservation for fertility preservation in females undergoing gonadotoxic cancer treatment:** Because cancer treatments have improved, resulting in long-term survival, procedures for maintaining long-term quality of life are of increasing interest. Females (children or adults) who have undergone systemic chemotherapy or whole-body radiation therapy especially may wish to preserve their ability to have children. A new option involves ovarian tissue cryopreservation. Before the patient undergoes treatment, clinicians collect ovarian tissue in a laparoscopic procedure requiring general anesthesia. Collected tissue is prepared to withstand the freezing process, and is then cryopreserved until completion of cancer treatment. Upon remission, the tissue is transplanted back into the patient to restore normal hormonal cycling and, if successful, fertility. This intervention was deemed by experts to have potential for high impact and had been in prior Potential High Impact reports dating to December 2013. Despite the emphasis placed on preserving fertility by most cancer centers treating adolescents and young adults with cancer, after tracking the procedure for more than 2 years in the horizon scanning system, we have archived it because of limited diffusion, low utilization, and limited access. Limited diffusion appears to be driven by insufficient accumulation of outcomes data and noncoverage by third-party payers because they consider ovarian tissue cryopreservation to be experimental. Thus, while the

intervention could still be important to individuals who can access it, overall unless it can diffuse more widely, its impact will remain limited.

Eligible Topics Not Deemed High Impact

In this section, we briefly discuss 12 interventions that were deemed to have no high-impact potential at this time based on experts' comments, poor outcomes in clinical trials, or no longer meeting Healthcare Horizon Scanning System requirements. We archived 10 of these interventions; the other 2 will be monitored to see whether additional data emerge that could change expert opinion.

- **Afatinib (Gilotrif®) for treatment of advanced head and neck cancer:** Experts commenting on afatinib for treating head and neck cancer agreed an unmet need exists for targeted interventions for patients whose disease progresses after first-line chemotherapy. However, because afatinib is an oral drug, it was not anticipated to affect substantially infrastructure or patient management and it is likely to be accepted by physicians and patients, who have limited treatment options, experts concurred. A couple of commenters were concerned about the outcomes from a clinical trial, stating that an observed extension in progression-free survival of less than 1 month is not an improvement that qualifies afatinib as an intervention that addresses an unmet need. Conversely, a clinician and a researcher argued in favor of afatinib as having potential to address the unmet need due to the lack of targeted interventions after first-line treatment. The researcher noted that patients with head and neck cancer treated with afatinib could show favorable outcomes that mirror those in patients with nonsmall cell lung cancer (NSCLC) treated with afatinib. Meanwhile, a clinician thought that afatinib has potential to improve outcomes in patients with a particular profile who show the greatest benefit from treatment. The available phase III data and commenters' opinions are that afatinib does not have high-impact potential at this time. We await additional data from ongoing phase III trials and will seek additional expert comments to determine whether it might have potential for high impact in the future.
- **Anamorelin for treatment of cancer-related cachexia/anorexia:** Although the initial data from the phase III trials are positive and indicate anamorelin has potential to address the unmet need, some experts commenting on this intervention thought the data were too preliminary and short-term (12 weeks) to know whether the drug will be effective long term. They also pointed out that cancer-related cachexia/anorexia is caused by a complex mechanism that is not fully understood; therefore, it seems unlikely anamorelin as a monotherapy would be able to fully address the problem. Besides the potential anamorelin has for treating cachexia, other factors such as patient education and behavior can be used to help patients improve quality of life and outcomes, one expert indicated. A secondary analysis of the phase III trial indicated that lean body mass increase in patients treated with anamorelin was correlated with a small increase in survival; however, no new clinical trial data showing efficacy have become available since the release of the topline data for the phase III trial, and the manufacturer has issued no statements regarding pursuit of regulatory approval in the United States. For these reasons, anamorelin was deemed to have no high-impact potential at this time. We will continue to track this topic for news of a U.S. regulatory filing or longer-term results from the phase III ROMANA3 trial.
- **Cabozantinib (Cometriq®) for treatment of renal cell carcinoma:** An unmet need exists for interventions to treat renal cell carcinoma (RCC) after angiogenesis inhibitors have been given and progression occurs, commenters expressed. Some commenters noted treatment with cabozantinib improved patient outcomes in the phase III METEOR trial. The study

demonstrated cabozantinib prevented disease recurrence for about 4 months; however, one commenter indicated the drug did not improve overall survival. Additionally, several commenters expressed concern about the reported adverse events and the need for dose reductions to address them. Because cabozantinib is an oral medication, most commenters agreed it would be easily adopted by physicians and patients while having little effect on health care infrastructure and patient management. However, a commenter with a clinical perspective noted that nivolumab may show superior clinical benefits, compared with cabozantinib. Therefore, nivolumab (Opdivo) may become the preferred treatment. Cabozantinib was considered to have little potential for high impact mainly because of its limited efficacy and adverse events; this topic was archived in November 2015.

- **Capsule endoscopy (PillCam Colon 2) for colorectal cancer screening:** Each year between 350,000 and 700,000 patients who were screened for colorectal cancer (CRC) have incomplete colonoscopies and require additional screening to identify potential cancerous polyps. For these patients, available options include repeat colonoscopy or computed tomography (CT), both of which can be expensive but are usually covered by insurance. Available data suggest that capsule endoscopy has potential to be a safe, effective, and affordable method to screen patients after incomplete colonoscopies, a commenter opined. However, the remaining commenters suggested that the capsule endoscopy clinical data failed to demonstrate superiority over CT for identifying cancer lesions and the device is not covered by major payers at this time, so costs for its use would be absorbed by patients and providers. Therefore, capsule endoscopy was deemed to have no high-impact potential and was archived in September 2015.
- **Denosumab (Xgeva®) for treatment of refractory hypercalcemia of malignancy:** Hypercalcemia of malignancy (HCM) affects between 20% and 30% of patients with cancer, and its onset decreases patient quality of life and increases mortality. Bisphosphates are the standard treatment for HCM, but 20% of patients do not respond; thus, a need exists for second-line agents to treat this small population, most commenters concurred. Although patients responded to denosumab after failing bisphosphate treatment, commenters questioned the effectiveness of denosumab, because data reported were from a small, uncontrolled study. However, commenters also noted the difficulties of conducting larger placebo-controlled studies to further test efficacy since the drug is already FDA-approved for other uses and is being used to treat patients. Therefore, denosumab was deemed to have no high-impact potential and was archived in November 2015.
- **High-intensity focused ultrasound systems (HIFU; Ablatherm®, Sonablate®) for treatment of localized prostate cancer:** Experts commenting on this topic indicated that deciphering the efficacy of these technologies was difficult because studies conducted in the United States did not compare it to standard of care. Also, the significantly high failure and complication rates being reported in studies undermine the safety and efficacy of HIFU for treating prostate cancer, two commenters noted. Based on the lack of effectiveness shown in ongoing studies and the availability of other focal therapies for treating localized prostate cancer, experts deemed HIFU to have no high-impact potential and these topics were archived in September 2015.
- **Obinutuzumab (Gazyva®) for treatment of indolent non-Hodgkin's lymphoma:** An unmet need exists for interventions for treating indolent non-Hodgkin's lymphoma, commenters agreed. Obinutuzumab is a next-generation antibody specific for the CD20 antigen, and trials compared its efficacy in combination with bendamustine versus bendamustine alone. Two commenters argued the study should have tested obinutuzumab against the first-generation CD20 antibody rituximab. Overall, commenters thought the

benefits of obinutuzumab were incremental to existing CD20 antibodies (e.g., rituximab, ofatumumab) and considered it to have no high-impact potential; this intervention was archived in November 2015 from the horizon scanning system.

- **Off-label vemurafenib for treatment of hairy cell leukemia:** Hairy cell leukemia is a rare type of leukemia, and treatments are available to which patients respond well. However, commenters were concerned that no treatment options are available for patients whose disease becomes refractory to standard treatments. Vemurafenib showed promising results; however, the conducted study reported only short-term outcomes. Commenters did not think vemurafenib had high-impact potential because of the rarity of the disease and the small number of affected patients who do not respond to initial treatment. This topic was archived in November 2015.
- **Ramucirumab (Cyramza®) for treatment of metastatic colorectal cancer:** Patients with CRC have limited options when the disease becomes treatment-refractory, and commenters unanimously agreed an unmet need exists for novel second- and third-line treatment options. Although FDA approved ramucirumab, available phase III data show it extends survival by fewer than 2 months and is associated with serious adverse events. Ramucirumab targets one of several pathways involved in developing CRC, and a commenter thought this could limit its efficacy. Another commenter stated that patient quality of life would be better with no treatment than with ramucirumab treatment. Overall, expert comments did not deem ramucirumab to have high-impact potential; the topic was archived in the Horizon Scanning system in November 2015.
- **Trifluridine tipiracil hydrochloride (TAS-102; Lonsurf®) for treatment-refractory metastatic colorectal cancer:** As CRC progresses to late stages, it becomes resistant to treatment; most commenters noted a large unmet need exists for options for treatment-refractory CRC. Although TAS-102 was approved by FDA and has few barriers for acceptance by physicians and patients, commenters suggested it has minimal potential to fulfill the unmet need because it improves survival by only about 2 months. A commenter with a clinical perspective also pointed out that if the phase III trial had compared TAS-102 with an antimetabolite instead of placebo, the improvement in patient outcomes would have been of even smaller magnitude. Commenters concurred that TAS-102 has no high-impact potential because it achieved only marginal survival improvement and would increase side effects and costs. TAS-102 was archived in November 2015 in the Horizon Scanning system.
- **Urocidin for treatment of nonmuscle bladder cancer:** Most commenters concurred an unmet need exists for interventions treating progressive bladder cancer after first-line therapy. This patient population has limited second-line options and patients have poor outcomes. Urocidin has potential to address the unmet need because its unique mechanism of action enhances immune responses against bladder cancer cells, two commenters thought. However, two other commenters argued that data from a noncomparative study showed no evidence that linked urocidin treatment with improved patient outcomes. Based on these comments, urocidin was considered to provide incremental improvement at best and have no high-impact potential. We archived this topic in August 2015 in the Horizon Scanning system.

Eligible Topics Deemed High Impact

Topics that emerged as having potential for high impact include a novel CRC screening test that offers a potential improvement upon existing screening technologies and novel drugs and biologics

with potential to improve patient outcomes. The conditions that these interventions address include solid tumors (breast cancer, CRC, gastric cancer, neuroblastoma, NSCLC, melanoma, and RCC) and hematologic malignancies (Castleman's disease, acute lymphoblastic leukemia [ALL], chronic lymphocytic leukemia [CLL], multiple myeloma, non-Hodgkin's lymphoma, and polycythemia vera). The group of therapeutic agents includes both small-molecule and biologic drugs.

The small-molecule drugs deemed to have high-impact potential are seven kinase inhibitors (crizotinib, ibrutinib, idelalisib, osimertinib, palbociclib, rociletinib, and ruxolitinib) targeting signaling pathways that researchers have observed to be involved in the pathogenesis of specific cancer types. In several instances, these drugs represent personalized approaches to treating cancer because they require genetic testing of patients' tumors and are intended to be used only in specific, molecularly defined cancer subtypes (i.e., crizotinib in *ROS1* mutation-positive NSCLC, osimertinib and rociletinib in *EGFR*^{T790M} mutation-positive NSCLC; palbociclib in estrogen receptor-positive breast cancer).

The biologic drugs deemed to have high impact potential are seven monoclonal antibodies (daratumumab, dinutuximab, elotuzumab, nivolumab, pembrolizumab, ramucirumab, and siltuximab), the engineered bi-specific antibody blinatumomab, and the oncolytic virus talimogene laherparepvec. The majority of these therapies involve the activation of an immune response against cancer through one of several mechanisms.

First, so-called checkpoint inhibitors (nivolumab, pembrolizumab) reportedly act by inhibiting a natural brake on the immune system that allows cancer cells to avoid an immune response. Checkpoint inhibitors are FDA approved for treating melanoma, NSCLC, and RCC; however, preliminary data indicate that this mechanism of action may be applicable to a wide variety of cancer types, and regulatory approvals in additional cancer types are anticipated in coming years.

Second, several of the monoclonal antibodies (i.e., daratumumab, dinutuximab, elotuzumab) are specific for molecules highly expressed by malignant cells, and antibody binding is thought to induce malignant cell death by activating the innate immune system. Lastly, both blinatumomab and talimogene laherparepvec represent novel immune-based mechanisms of action. Other monoclonal antibodies that are deemed to have high impact potential target molecules involved in promoting cancer growth and survival (e.g., targeting of interleukin 6 by siltuximab) or angiogenesis (e.g., targeting of vascular endothelial growth factor receptor 2 [VEGFR2] by ramucirumab).

Brief summaries of these topics are presented below.

Breast Cancer

Palbociclib (Ibrance) for Treatment of Estrogen Receptor-Positive Breast Cancer

- **Key Facts:** In 2015, the American Cancer Society estimated that about 75% of the anticipated 234,000 cases of invasive breast cancer in the United States would be estrogen receptor-positive (ER-positive). This subclass is characterized by overexpression of the estrogen receptor. Some of the available treatment options inhibit ER signaling by targeting the receptor directly or by blocking the pathway responsible for synthesizing the ER ligand. Although oncologists treat patients with alternating endocrine therapies to reduce the chance of drug resistance, disease recurs in a significant number of patients with ER-positive breast cancer. Therefore, a need exists for drugs targeting elements downstream of the ER pathway that have the potential to decrease the incidence of drug resistance. One of the early steps of cell proliferation is mediated by cyclin-dependent kinases (CDKs) 4 and 6 when they interact with cyclin D, which in turn inactivates the tumor suppressor protein, retinoblastoma (Rb). Upon phosphorylation by the CDK4/6-cyclin D complex, Rb releases

its inhibitory hold on the transcription factor E2F, which will begin to transcribe genes required for DNA synthesis, promoting cell-cycle progression. Palbociclib (Ibrance®) selectively inhibits CDK 4 and 6 and purportedly reduces drug resistance by blocking cell-cycle progression and inhibiting cancer cell proliferation. In February 2015, FDA approved palbociclib as first-line treatment for ER-positive/HER2-negative (human epidermal growth factor receptor 2–negative) breast cancer in combination with letrozole under FDA’s breakthrough therapy designation and priority review programs. Palbociclib is administered orally, daily, for 3 or 4 weeks, at a dose of 125 mg, and this regimen is being studied in combination with letrozole as first-line treatment of advanced ER-positive/HER2-negative breast cancer.

Finn and coworkers (2015) reported results from the phase II PALOMA-1 trial that compared palbociclib plus letrozole combination with letrozole alone in treatment-naïve postmenopausal women with advanced ER-positive/HER2-negative breast cancer. They reported that palbociclib increased progression-free survival and had an improved trend in overall survival. The most common adverse events reported with palbociclib were arthralgia, back pain, diarrhea, dyspnea, fatigue, leukopenia, nausea, neutropenia, and thrombocytopenia. These findings were the basis of a new drug application, which was granted priority review by FDA. Additionally, palbociclib is being studied in the adjuvant setting and as second-line treatment in patients whose disease has progressed after endocrine therapy. Results from PALOMA-3, a phase III trial testing palbociclib in combination with fulvestrant for treating endocrine therapy–relapsed, advanced, ER-positive/HER2-negative breast cancer, were reported by Turner and collaborators in June 2015. Investigators and an independent data monitoring committee determined that palbociclib plus fulvestrant significantly improved progression-free survival over placebo plus fulvestrant (9.2 vs. 3.8 months). The price for 21 capsules of 125 mg of palbociclib is about \$10,200. For third-party payer coverage, we found a prescription formulary and four medical policies that offer coverage for palbociclib, which like other cancer drugs is categorized as a specialty pharmaceutical requiring prior authorization for coverage. Two other CDK4/6 inhibitors—abemaciclib and ribociclib—are also in development for treating breast cancer and could compete with palbociclib.

- **Key Expert Comments:** Patients with metastatic ER-positive breast cancer have access to various types of endocrine therapy. However, in most cases the disease becomes resistant to treatment and progresses, which leaves patients with limited options that lack efficacy. Due to this unmet need, experts commenting on this intervention agreed palbociclib has potential to be an effective option for treating patients after endocrine therapy. Palbociclib targets elements downstream of the estrogen signaling pathway, which reduces the incidence of drug resistance and improves patient outcomes. Despite drug-related adverse events, experts opined patients will accept side effects if the drug extends their survival. The experts noted that broad adoption of palbociclib could be facilitated by its oral formulation and fact that it targets a novel cell-cycle checkpoint responsible for cancer development. They also thought palbociclib use is unlikely to affect health care infrastructure, patient management, or health disparities. One expert with research experience noted similar drugs are being investigated, which could also prove to be beneficial to patients.
- **High-Impact Potential:** Moderately high

Colorectal Cancer

Stool DNA Molecular Test (Cologuard) for Colorectal Cancer Screening

- **Key Facts:** New screening methods are highly desired that could improve the accuracy of existing noninvasive screening tests for CRC and increase the percentage of the population that undergoes recommended CRC screening. Research has demonstrated that cells undergo a number of genetic and epigenetic changes during malignant transformation, and detecting these changes may indicate a precancerous lesion or cancer. The Cologuard® stool DNA test is a molecular diagnostic designed to detect such changes in colon-derived cells sloughed off the intestinal walls and secreted with stool. Investigators studied the test in a 10,000-patient trial in which patients underwent Cologuard screening, fecal immunohistochemical testing (FIT, a standard noninvasive test that detects blood in stool), and colonoscopy. Imperiale and collaborators (2014) reported that, using colonoscopy findings as the gold standard, the sensitivity of Cologuard was 92.3% for CRC and 42.4% for precancerous lesions. These results compared favorably to the sensitivity of FIT, which was 73.8% and 23.8% for CRC and precancerous lesions, respectively. However, the reported specificity of Cologuard was lower than that of FIT: 86.6% versus 94.9%.

FDA approved Cologuard as a CRC screening option in August 2014, and the retail cost of the test has been reported as \$600. The Cologuard test underwent a parallel review by FDA and the U.S. Centers for Medicare and Medicaid Services (CMS) so that their decisions closely coincided. In October 2014, CMS issued its final national coverage determination for Cologuard, which covers use of the test once every 3 years. More recently, several third-party payers have made positive coverage determinations for non-Medicare beneficiaries.

- **Key Expert Comments:** Overall, experts suggested that the large number of screening-eligible patients who are not compliant with screening recommendations and the limited sensitivity of existing noninvasive test methods represents an important unmet need that a novel noninvasive test such as Cologuard could address. However, some commenters questioned the extent to which patients would opt for Cologuard-based screening, given the relatively high cost and requirement that patients collect stool samples. Additionally, experts commenting were divided as to the extent to which Cologuard improves detection rates relative to tests based on detecting blood in stool.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Gastric Cancer

Ramucirumab (Cyramza) for Treatment of Gastric Cancer

- **Key Facts:** Although surgical techniques, radiotherapy, and chemotherapy are available for patients with gastric cancer, outcomes remain poor because the cancer is locally advanced or metastatic in most patients at the time of diagnosis. Researchers have reported that gastric cancer progression depends heavily on vascular and epidermal growth factor pathways, and they have focused on developing drugs that target such pathways. Standard first-line therapy usually includes a combination of fluoropyrimidine/platinum-based chemotherapy with targeted drugs. Unfortunately the cancer progresses in most cases. VEGFR2 has a pivotal role in forming most blood vessels involving vascular endothelial growth factor pathways, and blocking this receptor could lead to improved outcomes in patients with advanced gastric cancer. In studying ramucirumab (Cyramza®), which is an antibody against VEGFR2, researchers have reported results from two studies using the agent as

monotherapy or combination therapy with paclitaxel for treating advanced gastric cancer. The REGARD trial studied patients whose disease had progressed after chemotherapy. Results from Fuchs et al. (2014) for the 355-patient, placebo-controlled trial showed improved median overall survival (5.2 vs. 3.8 months), and treatment (median 4 doses) was generally well tolerated. Reported common adverse events were hypertension and diarrhea. The RAINBOW trial studied ramucirumab in combination with paclitaxel for treating gastric cancer. As reported by Wilke et al. (2014), overall survival increased by 2.27 months, but adverse events were twice as severe in the combination therapy as in the paclitaxel-alone group. These events included abdominal pain, anemia, asthenia, fatigue, hypertension, leukopenia, and neutropenia.

Basing its decision on results from the REGARD trial, FDA approved ramucirumab in April 2014 for treating advanced gastric cancer or gastroesophageal junction adenocarcinoma, as monotherapy after fluoropyrimidine/platinum-based chemotherapy. Positive results from the RAINBOW trial led to a second approval, for ramucirumab in combination with paclitaxel, in November 2014. The labeling includes a boxed warning about increased risk of hemorrhage, including severe and sometimes fatal events. Ramucirumab is administered intravenously at a dosage of 8 mg/kg every 2 weeks until disease progression or toxicity limits further treatment. An adult of about 70 kg (154 lb) would require about 560 mg per dose. In May 2015, six vials of Cyramza 100 mg/10 mL reportedly cost about \$6,300—an amount sufficient for about one treatment. A search of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 6 policies regarding ramucirumab as medically necessary for treating patients with gastric cancer or gastroesophageal junction adenocarcinoma whose disease has progressed after fluoropyrimidine/platinum-based chemotherapy.

- **Key Expert Comments:** Most experts commenting on ramucirumab agreed that a need exists for new therapies for advanced gastric cancer because of the limited options available. Although ramucirumab showed efficacy in patients with gastric cancer, four experts thought it has only limited potential to fulfill this need because survival was marginally increased and the benefits might not outweigh the increase in adverse events. However, two experts anticipate that treatment with other combination therapies including ramucirumab could potentially have survival benefits longer than those reported in the latest clinical trials.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Hematologic Malignancies

Blinatumomab (Blincyto) for Treatment of Acute Lymphoblastic Leukemia

- **Key Facts:** For adult patients with recurrent or refractory ALL, prognosis is poor; median overall survival is only several months and the majority of these patients will die of their disease. No consensus on the standard of care for this patient population has been established, and substantial interest exists in novel methods for treating the disease. Blinatumomab (Blincyto®) is the first in a new class of anticancer treatments known as bi-specific T-cell engagers (BITEs), which purportedly promote the interaction of T cells with cancer cells, leading to cancer cell destruction. Topp and colleagues reported data in 2015 from a single-arm trial of blinatumomab in adult patients with recurrent/refractory B-precursor ALL. In this trial, 43% of patients (81 of 189) achieved a complete response or complete response with partial hematologic recovery within the first 2 cycles of

blinatumomab treatment. Basing its decision on these results and using its accelerated approval pathway, FDA approved blinatumomab in December 2014 for treating patients with Philadelphia chromosome–negative, recurrent or refractory B-cell precursor ALL. Blinatumomab’s prescribing information carries a black box warning about the potential for severe adverse events such as cytokine release syndrome and neurological toxicities, which occurred in 2% and 11%, respectively, of patients treated with blinatumomab. Additionally, the prescribing information notes that as a condition of the accelerated approval, the potential clinical benefit of blinatumomab inferred from a rate of complete response in the single-arm trial must be confirmed in a larger randomized trial. Blinatumomab’s developer reported that blinatumomab would be priced at about \$178,000 for a typical patient treatment consisting of two 6-week treatment cycles.

- **Key Expert Comments:** Available treatments for ALL have significant shortcomings, representing a substantial unmet need, according to commenters. Given this need for novel treatments and the promising responses seen in initial trials of blinatumomab, expert comments indicated that the drug is likely to be adopted widely by both patients and physicians. However, experts also cautioned that randomized controlled trials (RCTs) of blinatumomab would be needed to confirm the potential clinical benefit. Additionally, as a drug given in a standard ALL treatment setting to a small number of patients, blinatumomab was not seen by experts commenting as causing significant shifts in health care infrastructure or patient management.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Ibrutinib (Imbruvica) and Idelalisib (Zydelig) for Treatment of Non-Hodgkin’s Lymphomas

- **Key Facts:** B-cell non-Hodgkin’s lymphomas (NHLs), such as CLL and Waldenström’s macroglobulinemia, often respond well to first-line therapy; however, most patients experience recurrence. In this situation, available therapies have limited efficacy. Additionally, certain molecularly defined subtypes, such as CLL harboring a deletion in the short arm of chromosome 17, respond poorly to standard therapies. New agents to treat these cancers are highly desired. Recent research has identified the kinases BTK and phosphoinositide 3-kinase delta (PI3K-delta) as potential targets for treating B-cell malignancies.

Ibrutinib (Imbruvica®) is an oral, first-in-class Bruton’s tyrosine kinase (BTK) inhibitor under study for treating a wide range of B-cell malignancies. Initial FDA approvals of ibrutinib for treating CLL and Waldenström’s macroglobulinemia were based on data from single-arm studies: in 2013, Byrd and coauthors reported a 71% response rate in patients with recurrent or refractory CLL, and in 2015, Treon and coauthors reported a 90.5% response rate in patients with previously treated Waldenström’s macroglobulinemia. More recently, data have been reported from three randomized controlled studies of ibrutinib in treating CLL. In 2014, Byrd and coauthors reported results from an open-label, randomized controlled trial of ibrutinib versus the CD20 antibody ofatumumab for treating patients with recurrent/ refractory CLL (the RESONATE trial). In this trial, ibrutinib significantly improved overall survival compared with ofatumumab (hazard ratio [HR], 0.434; 95% confidence interval [CI], 0.238 to 0.789; p=0.0049). Subsequently, in 2015, Chanan-Khan and colleagues reported results from a double-blind, randomized controlled trial of ibrutinib in combination with bendamustine and rituximab compared with bendamustine and rituximab alone for treating patients with recurrent/refractory CLL (the HELIOS trial). In this trial, adding ibrutinib to bendamustine/rituximab resulted in a statistically significant

improvement in progression-free survival (HR, 0.203; 95% CI, 0.150 to 0.276; $p < 0.0001$). Lastly, also in 2015, Tedeschi and coauthors reported results from an open-label, randomized controlled trial of ibrutinib versus chlorambucil in treating patients 65 years of age or older with treatment-naïve CLL (the RESONATE-2 trial). In this trial, progression-free survival was improved significantly in the ibrutinib arm (HR 0.16; 95% CI, 0.09 to 0.28, $p < 0.0001$).

FDA has approved ibrutinib for four NHL indications: (1) patients with mantle cell lymphoma who have received at least one prior therapy; (2) patients with CLL who have received at least one prior therapy; (3) patients with CLL harboring a chromosome 17p deletion; and (4) patients with Waldenstrom's macroglobulinemia. The labeled dosage for mantle cell lymphoma is 560 mg, once daily, and for CLL and Waldenstrom's macroglobulinemia, 420 mg, once daily. The retail price for ibrutinib at the recommended dose for treating CLL and Waldenstrom's macroglobulinemia is about \$9,900 per month.

Idelalisib (Zydelig®) is an oral, first-in-class, PI3K-delta inhibitor also under study for treating a wide range of B-cell malignancies. Investigators have reported results from three RCTs of idelalisib in treating patients with recurrent/refractory CLL. In 2014, Furman and collaborators reported that adding idelalisib to standard treatment with rituximab improved both progression-free survival (85% reduction in risk of progression or death) and the overall response rate (81% rituximab plus idelalisib vs. 13% rituximab plus placebo). In 2015, Jones and colleagues reported that combining idelalisib and ofatumumab resulted in an improvement in progression-free survival relative to ofatumumab monotherapy (16.3 vs. 8.0 months; HR, 0.27; $p < 0.0001$). Lastly, in 2015, Zelenetz and colleagues reported that the adding idelalisib to chemoimmunotherapy with bendamustine and rituximab resulted in an improvement in progression-free survival relative to bendamustine and rituximab plus placebo (23 vs. 11 months; HR, 0.33, $p = 2.8 \times 10^{-14}$). Separately, investigators have reported results from a single-arm trial of idelalisib for treating recurrent/refractory indolent NHL. In 2014, Gopal and colleagues reported that a response rate of 57% was observed for idelalisib monotherapy.

In July 2014, FDA approved idelalisib for treating recurrent/refractory CLL in combination with rituximab and for two forms of recurrent/refractory indolent NHL (follicular lymphoma and small lymphocytic lymphoma) as a monotherapy. The retail price for idelalisib at the recommended dose of 150 mg twice daily is about \$8,200 per month.

- **Key Expert Comments:** Overall, experts thought a significant need exists for better and novel treatments for B-cell lymphomas and that response rates observed in initial trials of ibrutinib and idelalisib indicated that the drugs have significant potential to improve patient outcomes. However, experts commenting suggested that further confirmatory studies are needed, particularly studies comparing ibrutinib and idelalisib to alternatives. Experts noted as significant the relatively benign side-effect profiles of ibrutinib and idelalisib and their potential to be used for extended periods in treating several B-cell malignancies.
- **High-Impact Potential:** High

Monoclonal Antibodies (Daratumumab [Darzalex], Elotuzumab [Empliciti]) for Treatment of Multiple Myeloma

- **Key Facts:** About 11,000 people in the United States die of multiple myeloma each year, and a need exists for novel treatments with the potential to improve outcomes for patients with the disease. Daratumumab [Darzalex®] and elotuzumab [Empliciti™] are two drugs approved by FDA in November 2015 for treating patients who have multiple myeloma and are the first monoclonal antibodies approved for treating this disease. Both drugs target

proteins expressed at high levels by myeloma cells (CD38 for daratumumab and SLAMF7 for elotuzumab). Binding of the antibody to its targets is thought to induce myeloma cell death by activating cells of the innate immune system.

FDA approval of daratumumab was based on data from two single-arm clinical trials: the phase II Sirius trial and the phase I/II GEN501 trial. In 2015, Lonial and colleagues presented results from the Sirius trial, which enrolled patients with multiple myeloma who had received at least three lines of therapy including both an immunomodulatory drug and a proteasome inhibitor. For patients who received the 16 mg/kg dose (n=106), investigators reported an overall response rate of 29.2%. Also in 2015, Lokhorst and colleagues published results from the GEN501 trial, which enrolled patients with multiple myeloma that was refractory to two or more lines of therapy. For patients who received the 16 mg/kg dose (n=42), investigators reported an overall response rate of 36%.

FDA approval of elotuzumab was based on data from the randomized, phase III ELOQUENT-2 trial, in which patients with multiple myeloma who had received one to three previous therapies were randomly assigned to treatment with either elotuzumab in combination with lenalidomide and dexamethasone (n=321) or to treatment with lenalidomide and dexamethasone alone (n=325). In results published in 2015, Lonial and colleagues reported progression-free survival of 19.4 months for patients in the elotuzumab arm compared with 14.9 months in the control arm. Additionally, an increase in the overall response rate was observed in the elotuzumab arm compared with the control arm: 79% and 66%, respectively.

Patients with multiple myeloma already incur high costs during the course of their treatment, and adding daratumumab and elotuzumab to the set of treatment options is likely to increase costs further. The cost for year one of treatment with daratumumab or elotuzumab is reportedly about \$136,000 and \$142,000, respectively.

- **Key Expert Comments:** Overall, experts commenting suggested that the improvements in progression-free survival observed for daratumumab and elotuzumab in patients with recurrent/refractory multiple myeloma represent an important advance in treating this incurable disease. For these reasons, the majority of experts commenting envisioned that the drugs would be widely adopted for treating these patients. Additionally, experts suggested that these drugs could add substantially to the cost of treating patients who have multiple myeloma, potentially worsening any existing health disparities based on economic status or access to insurance coverage. Although these drugs are the first infused monoclonal antibody treatments for multiple myeloma, commenters did not believe that their use would cause substantial disruption to health care facility staffing or infrastructure because of the familiarity of health care workers with using infused therapies for cancer treatment.
- **High-Impact Potential:** Moderately high

Ruxolitinib (Jakafi) for Treatment of Polycythemia Vera

- **Key Facts:** Polycythemia vera is a myeloproliferative neoplasm that affects about 100,000 people in the United States. Only one treatment for the disease is FDA approved, and an unmet need exists for novel, effective therapies, particularly in patients with polycythemia vera whose symptoms are inadequately controlled by treatment with hydroxyurea. The FDA-approved drug, ruxolitinib, is an orally administered, small-molecule inhibitor of two protein kinases—Janus kinase 1 and 2—that play central roles in regulating myeloid lineages. Overactivation of Janus kinase pathway signaling has been linked to pathogenesis of the disease, and about 90% of polycythemia vera cases harbor an activating mutation in the gene encoding Janus kinase 2 (i.e., *JAK2V617F*). Use of ruxolitinib in treating patients with

polycythemia vera whose disease is inadequately controlled by hydroxyurea has been studied in two phase III clinical trials: RESPONSE and RELIEF. In the RESPONSE trial, ruxolitinib compared with physician's choice of best available therapy demonstrated a significant increase in the percentage of patients achieving both hematocrit control without phlebotomy and a reduction in spleen volume of at least 35% (ruxolitinib 21% vs. best available therapy 1%; $p < 0.0001$). In the RELIEF trial, ruxolitinib compared with continued treatment with hydroxyurea demonstrated a trend towards improved symptom control, but the difference was not statistically significant. The percentage of patients achieving a 50% or greater reduction in a patient-reported symptom severity score was 43.4% in the ruxolitinib arm and 29.6% in the hydroxyurea arm ($p = 0.139$).

In December 2014, FDA approved the use of ruxolitinib for treating patients with “polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea,” making ruxolitinib the first drug to be approved for treating polycythemia vera. FDA had previously approved ruxolitinib for treating a related myeloproliferative neoplasm, myelofibrosis, and ruxolitinib is available commercially. The retail cost for 1 year of ruxolitinib treatment is about \$120,000 (or \$9,995 per month).

- **Key Expert Comments:** Overall, experts commenting on this intervention believe that ruxolitinib has potential to meet a significant unmet need, given the significant morbidity that patients with polycythemia vera experience and the lack of approved treatments. In terms of improving health, the majority of commenters suggested ruxolitinib has substantial potential to improve treatments for patients with polycythemia vera, citing the efficacy demonstrated in the RESPONSE trial, the relatively benign safety profile, and the lack of existing safe and effective treatments. However, experts also suggested that because of its routine mode of administration, ruxolitinib's adoption for treating patients with polycythemia vera would have only minimal impacts on health care infrastructure and patient management. Based on these mixed perspectives on the part of experts commenting, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Siltuximab (Sylvant) for Treatment of Multicentric Castleman's Disease

- **Key Facts:** Multicentric Castleman's disease is a rare lymphoproliferative disorder without effective treatment options. Siltuximab is a monoclonal antibody specific for interleukin-6 (IL-6), a cytokine whose upregulation is thought to underlie the pathogenesis of multicentric Castleman's disease. Treatment with siltuximab purportedly neutralizes IL-6, thereby improving disease symptoms. In results of a randomized, placebo-controlled trial reported by Wong et al. (2013), patients treated with siltuximab demonstrated significantly improved tumor and symptom response (34% siltuximab vs. 0% placebo; $p = 0.0012$). Siltuximab was generally well tolerated, with similar rates of adverse events reported in both treatment and placebo arms of the trial.

In April 2014, FDA approved siltuximab for treating this disease. According to the prescribing information, siltuximab is indicated for treating patients “with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.” The drug is administered by intravenous infusion every 3 weeks, until disease progression, at a dose of 11 mg/kg given over 1 hour. In May 2015, cost was reportedly \$860 for a 100 mg vial. An adult of about 70 kg would require about 770 mg, or 8 vials, at about \$7,000 per dose.

- **Key Expert Comments:** Overall, experts concurred that siltuximab has potential to fill a significant unmet need of patients with multicentric Castleman's disease, given results from the clinical trial supporting its approval and the fact that FDA has approved no other therapies for this indication. However, siltuximab's overall impact is limited by the small size of the eligible patient population, the lack of any substantial changes to patient management or health care facility infrastructure, and the preliminary nature of the data on a therapy that could potentially be taken for extended periods.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Kidney Cancer

Nivolumab (Opdivo) for Treatment of Advanced Renal Cell Carcinoma

- **Key Facts:** According to the National Cancer Institute, RCC forms in the lining of small tubules in the kidney that filter the blood and remove waste products. Renal pelvis carcinoma is another type of kidney cancer that forms in the center of the kidney where urine collects. The American Cancer Society has estimated that kidney cancer (including RCCs and carcinomas of the renal pelvis) in the United States in 2015 would be seen in 61,560 new cases and lead to 14,080 deaths. About 85% of RCCs are adenocarcinomas; most of the rest are transitional cell carcinomas of the renal pelvis. RCC can often be cured if it is diagnosed and treated when still localized to the kidney and to the immediate surrounding tissue. However, about 30% of RCCs are metastatic when first diagnosed and need to be treated with therapies that target angiogenesis or the mammalian target of rapamycin (mTOR) signaling pathway. Unfortunately patients with progressive disease after first-line therapy have limited options and poor outcomes; thus, a need exists for effective second-line treatments. Nivolumab (Opdivo®) is a monoclonal antibody that targets the programmed death-1 (PD-1) receptor, which inhibits immune checkpoints that suppress anticancer immune responses. Basing its decision on results from the phase III CheckMate 025 trial, FDA granted nivolumab breakthrough therapy status in September 2015, and then approved it through its priority review program in November 2015. The anticipated cost of 100 mg of nivolumab is about \$2,500, and it is likely third-party payers will update their policies to cover nivolumab for its FDA-approved indication.

Nivolumab is under study as first-line treatment (CheckMate 214) and as second-line treatment (CheckMate 025) for treating RCC. In 2015, Motzer and collaborators reported results from the phase III CheckMate 025 trial, which showed improvement in its primary endpoint of overall survival (25.0 vs. 19.6 months), as compared with everolimus. Nivolumab also demonstrated improvement in response rates (25% vs. 5%) and progression-free survival (4.6 vs. 4.4 months), although the latter did not reach statistical significance. Patients who received nivolumab treatment also experienced fewer drug-related adverse events than those receiving everolimus. Anemia and fatigue were the most common nivolumab-related adverse events.

- **Key Expert Comments:** Despite nivolumab showing greater efficacy than everolimus in a clinical trial, two experts with clinical backgrounds thought nivolumab has only small potential to fulfill the unmet need. They thought that even with durable responses, there was minimal improvement in progression-free survival. In contrast, the other experts considered the efficacy of nivolumab to be better than that of everolimus and thought it holds promise for patients who have limited options when their disease does not respond to standard treatments. Additionally, an expert commented that patients will appreciate a 6-month extension in their life, which is rarely observed with most new cancer drugs. Because

options are limited after patients no longer respond to treatment, experts anticipate clinicians and patients will accept nivolumab for treating RCC. Because it is an intravenous drug instead of an oral one, nivolumab will cause a small change in patient management but will not disrupt health care infrastructure. Nivolumab is expensive, but its FDA approval may lead to reimbursement by third-party payers, and there are assistance programs to help uninsured and underinsured patients.

- **High-Impact Potential:** Lower end of the high-impact-potential range

Lung Cancer

Checkpoint Inhibitors (Nivolumab [Opdivo], Pembrolizumab [Keytruda]) for Treatment of Non-small Cell Lung Cancer

- **Key Facts:** Lung cancer is the second most common cancer diagnosed in the United States and is the leading cause of cancer death. Lung cancer was expected to be diagnosed in an estimated 221,200 Americans and an estimated 158,040 were expected to die of the disease in 2015. NSCLC accounts for about 75% of lung cancers and has a 5-year survival rate of 2% to 13%; thus, a need exists for interventions that can improve patient outcomes. NSCLC among other types of cancer has adapted a mechanism to avoid being detected by the immune system by activating the checkpoint pathway via the programmed death-1 (PD-1) receptor. Cancer cells overexpress the ligand of PD-1 (PD-L1) and diminish the antitumor response of immune T cells upon binding to PD-1. Nivolumab (Opdivo) and pembrolizumab (Keytruda®) are monoclonal antibodies specific for PD-1 that prevent interaction with PD-L1, thus potentially improving patient survival by disrupting the immune tolerance signal between PD-1 and PD-L1 in immune and tumor cells, respectively. In February 2015 and after priority review, FDA approved nivolumab for treating NSCLC that has progressed after platinum-based chemotherapy. Results from the phase III CheckMate 017 and the phase II CheckMate 063 trials were the basis for nivolumab's approval. In October 2015, FDA granted accelerated approval to pembrolizumab based on results from the phase I KEYNOTE-001 trial after earlier granting breakthrough therapy status.

Spigel and coworkers and Paz-Ares and coauthors presented results from the phase III CheckMate 017 and CheckMate 057 trials at the 2015 American Society of Clinical Oncology annual meeting. Patients with squamous NSCLC enrolled in the CheckMate 017 trial were treated with nivolumab or docetaxel, and the nivolumab group showed a statistically significant improvement in overall survival (9.2 vs. 6.0 months), progression-free survival (3.5 vs. 2.8 months), and response rate (20% vs. 9%). Meanwhile, patients with nonsquamous NSCLC in the CheckMate 057 trial who received nivolumab had improved overall survival over patients given docetaxel (12.2 vs. 9.4 months) and improved response rate (19.2% vs. 12.4%), but not longer progression-free survival (2.3 vs. 4.2 months), which could be related to PD-L1 expression. Patients with NSCLC are treated intravenously with 3 mg/kg of nivolumab once every 2 weeks until disease progression or unacceptable toxicity. Results published by Garon and coworkers in 2015 demonstrated that patients treated with pembrolizumab (2 mg/kg once every 3 weeks, 10 mg/kg once every 2 weeks, or 10 mg/kg once every 3 weeks) who expressed PD-L1 in 50% or more of cancer cells had superior outcomes, as compared with all enrolled patients. The validation group (>50% PD-L1) experienced response rates of 45.2%, a median progression-free survival of 6.3 months, and had not reached median overall survival at the data cutoff point. The most common drug-related adverse events manifested by patients receiving pembrolizumab were appetite loss, fatigue, and pruritus.

The reported cost of nivolumab and pembrolizumab is about \$2,500 for 100 mg and about \$6,600 for 150 mg, respectively, which per year would add up to about \$136,500 for nivolumab and \$112,200 for pembrolizumab. Third-party payers that cover nivolumab require preauthorization and will likely cover the recently approved pembrolizumab when health policies are updated.

- **Key Expert Comments:** Overall, most experts commenting on these interventions thought nivolumab and pembrolizumab have significant potential to improve outcomes in patients with NSCLC, who currently have limited treatment options. Further, if results from additional studies continue to be favorable and the role of PD-L1 in cancer is better understood, checkpoint inhibitors have the potential to offer more benefit than standard treatments. If the available clinical data suggest they can be novel options for treatment-resistant NSCLC, experts anticipate, nivolumab and pembrolizumab will be widely adopted by physicians and patients. In a contrasting opinion, some experts thought that the onset of serious adverse events caused by immunotherapy could be a hurdle for adoption. Because they are administered intravenously, checkpoint inhibitors will not affect health care infrastructure or patient management. Experts agreed checkpoint inhibitors are very expensive and have a high potential to affect health care costs; whether costs will be absorbed mostly by third-party payers or patients remains to be determined because it will depend on coverage and any discounts negotiated by payers with the company.
- **High-Impact Potential:** Higher end of the high-impact-potential range

Crizotinib (Xalkori) for Treatment of *ROS1*-Positive Nonsmall Cell Lung Cancer

- **Key Facts:** Lung cancer is caused by abnormal or uncontrolled cell growth in the lungs or bronchus; it is one of the most common cancers diagnosed in the United States and the leading cause of cancer death. In 2015, lung cancer was expected to be diagnosed in an estimated 221,200 Americans and an estimated 158,040 were expected to die of the disease. The majority of lung cancers take one of two forms: NSCLC, which accounts for 85% of cases, and small cell lung cancer (SCLC), which accounts for about 15% of cases. Between 1% and 2% of NSCLCs are caused by a gene fusion between the *ROS1* proto-oncogene and various other genes resulting in constitutive activity that causes cells to proliferate uncontrollably. Because patients with *ROS1*-positive NSCLC have disease that does not respond to conventional therapy, a need exists for therapies targeting *ROS1* alterations. Crizotinib (Xalkori®) is a tyrosine kinase inhibitor FDA approved in 2011 for treating *ALK*-positive NSCLC, which has also shown activity in *ROS1*-positive NSCLC and was granted breakthrough therapy status by FDA in April 2015. Two cohorts of patients with *ROS1*-positive NSCLC participating in the PROFILE 1001 and EUROS1 trials showed favorable response rates (72% and 80%, respectively) and progression-free survival (19.2 and 9.1 months) after receiving crizotinib treatment. It was well tolerated and caused manageable adverse events, which included constipation, diarrhea, edema, nausea, vision disorder, and vomiting. Third-party payers have policies that cover crizotinib for treating *ALK*-positive NSCLC and if it receives an expanded indication for treating *ROS1*-positive NSCLC, it is likely to also be reimbursed in that patient population.
- **Key Expert Comments:** Most experts commenting on crizotinib concluded it has potential to benefit patients with *ROS1*-positive NSCLC, noting that its high efficacy and low toxicity will allow patients to have extended lives without affecting their quality of life. A clinician noted crizotinib falls within the most recent oncology model for targeted therapies, which involves developing highly effective treatments for a small number of patients. In a

contrasting opinion based on poor outcomes in patients with NSCLC, an expert with a research perspective did not think crizotinib has much potential to fulfill the unmet need. Crizotinib is an oral drug for treating a small number of patients and data from clinical trials have demonstrated it is safe and effective; thus, crizotinib will face no barriers for acceptance and will be unlikely to affect health delivery or patient management unless diagnostic testing becomes a limiting factor for patient access to crizotinib.

- **High-Impact Potential:** Lower end of the high-impact-potential range

Next Generation EGFR Inhibitors (Osimertinib [Tagrisso], Rociletinib) for Treatment of Nonsmall Cell Lung Cancer

- **Key Facts:** Fifteen to 30% of NSCLC cases harbor an activating mutation in the gene encoding the epidermal growth factor receptor (EGFR), with higher rates in Asians, women and never smokers. EGFR inhibitors have improved outcomes for patients with *EGFR* mutation-positive NSCLC relative to cytotoxic chemotherapy; however, these inhibitors have limitations such as frequently developed treatment resistance and toxicity from inhibiting nonmutated EGFR in normal tissues. Substantial interest exists in developing novel targeted therapies with the potential to overcome these shortcomings. Osimertinib and rociletinib are two such drugs being studied for treating NSCLC. Both drugs are next-generation EGFR inhibitors that are highly selective for mutated forms of EGFR. Because of this selectivity, developers purport that these drugs may exhibit improved adverse event profiles relative to available EGFR inhibitors. Additionally, both drugs have demonstrated activity against a variant of EGFR (EGFR^{T790M}) that is the cause of EGFR-inhibitor resistance in over half of all cases; these drugs could have clinical utility in patients whose disease has progressed during treatment with first-generation EGFR inhibitors, in particular those patients whose disease harbors the T790M mutation.

Results for osimertinib have been reported from two single-arm clinical trials, AURA and AURA2, which enrolled patients with metastatic NSCLC previously treated with an EGFR inhibitor and confirmed to harbor the T790M resistance mutation. At the 2015 World Conference on Lung Cancer, Yang and colleagues presented results of an AURA trial expansion cohort that enrolled 201 such patients and reported an overall response rate of 58% among evaluable patients. At the same meeting, Mitsudomi and colleagues presented results for the AURA2 trial that enrolled 210 such patients and reported an overall response rate of 64% among evaluable patients. Basing its action on data from these trials, FDA granted osimertinib (80 mg once daily) accelerated approval in November 2015 for use in treating patients with metastatic *EGFR*^{T790M} mutation-positive NSCLC whose disease has progressed on or after EGFR inhibitor therapy. The FDA-approved indication specifies that T790M mutation status must be detected using an FDA-approved test, and the agency approved a companion diagnostic test for osimertinib at the same time the drug was approved. The drug's manufacturer has reportedly priced osimertinib at \$12,750 per month of treatment.

Rociletinib results have been reported from one single-arm clinical trial, the TIGER-X trial, which enrolled patients with metastatic NSCLC previously treated with an EGFR inhibitor and confirmed to harbor the T790M resistance mutation. In 2015, Sequist and colleagues published preliminary results from this trial, reporting an overall response rate of 59% among patients receiving an active dose of the drug. The manufacturer submitted a new drug application to FDA for rociletinib based on this data, and a decision date was set for March 2016. However, the company subsequently indicated that FDA had requested additional data and that this revision to the new drug application could delay a decision on

the drug's approval. Additionally, the manufacturer noted in this announcement that the confirmed response rate for the drug was lower than the figure originally reported by Sequist and colleagues, which included both confirmed and unconfirmed responses.

- **Key Expert Comments:** Overall, experts suggested that osimertinib and rociletinib demonstrate substantial promise in treating patients with T790M mutation–positive NSCLC, a patient population for which an active targeted therapy had long been sought. Basing their opinions on these promising results, the majority of commenters suggested that the drugs would be widely adopted; however, they also cautioned that long-term studies incorporating comparator arms would be needed to confirm the drugs' clinical benefit. As orally administered medications, the drugs' use was not envisioned to require substantial disruption to health care facility staffing or infrastructure or patient management; however, repeat biopsies and additional genetic testing used to determine T790M mutation status could cause a moderate shift, according to some commenters.
- **High-Impact Potential:** Moderately high

Neuroblastoma

Dinutuximab for Treatment of Neuroblastoma

- **Key Facts:** Neuroblastoma is a malignant cancer that begins in immature neural cells (i.e., neuroblasts) of the sympathetic nervous system, developing primarily in sympathetic spinal ganglia near the neck, chest, or pelvis. Neuroblastoma occurs most often in early childhood; two-thirds of cases occur in children 5 years of age or younger. Each year, 700–800 cases of neuroblastoma are diagnosed in the United States. This makes up 7% to 10% of all childhood cancers, but accounts for 50% of all infant cancers. Rates are slightly higher in boys than in girls. Despite increasing overall survival rates, most patients have metastatic disease when neuroblastoma is first diagnosed, which is often aggressive, difficult to treat, and associated with poor outcomes. The glycolipid disialoganglioside (GD2) is uniformly expressed in neuroblastoma cells while its expression in normal tissues is limited. The GD2 monoclonal antibody dinutuximab (Unituxin™) has potential to fulfill the unmet need for patients with recurrent high-risk neuroblastoma after induction therapy and autologous stem cell transplantation. Evidence suggests dinutuximab causes neuroblastoma cell death by binding to GD2 and triggering complement- or antibody-dependent cytotoxicity. GD2 overexpression allows neuroblastoma cells to interact with the extracellular matrix and promote spread to other tissues. Therefore, by blocking GD2, dinutuximab may also prevent cells from metastasizing. In clinical trials, 5 cycles of dinutuximab are administered intravenously at a dose of 25 mg/m² on days 1–4 of a 28-day cycle in combination with interleukin-2 (IL-2) and granulocyte-macrophage colony-stimulating factor (GM-CSF), concomitantly with 6 cycles of isotretinoin.

In September 2010, Yu and collaborators published results from the phase III ANBL0032 trial, which demonstrated dinutuximab improved event-free progression and overall survival by 20% and 9%, respectively, as compared with standard therapy alone. Unfortunately, dinutuximab caused a higher rate of drug-related events, which included pain (52%), hypersensitivity (25%), and capillary leak syndrome (23%). In contrast, when Ozkaynak and collaborators presented additional safety and efficacy data at the 2014 American Society of Clinical Oncology annual meeting, they showed extending the infusion time from 5.75 to 10 hours led to fewer dinutuximab-related adverse events. Meanwhile, event-free survival and overall survival remained unchanged. Initially, dinutuximab was developed and tested by the Children's Oncology Group through funding from the National

Cancer Institute, which later began a collaboration with United Therapeutics Corp. to continue late clinical development and regulatory submissions of dinutuximab. In March 2015, basing its decision on results from the phase III ANBL0032 trial, FDA approved dinutuximab in combination with IL-2 and GM-CSF for treating high-risk neuroblastoma that responds to first-line multimodal therapy. Because dinutuximab became commercially available only recently, no pricing, coverage, coding, or payment information is available. However, third-party payers are likely to reimburse dinutuximab once their policies are updated.

- **Key Expert Comments:** Despite the small number of patients who develop neuroblastoma each year, patient outcomes are very poor because most cases are metastatic at the time of diagnosis, and the disease has a high recurrence rate. Overall, experts agreed dinutuximab has moderate potential to address the unmet need. Even with strong results showing survival surpassing 2 years, an expert thought further data are needed to assess patient quality of life. Another expert stated the efficacy of dinutuximab may be associated with its specificity for the neuroblastoma antigen GD2. Although additional safety and efficacy data for dinutuximab are needed, the available survival outcomes were sufficient for experts to suggest dinutuximab will be adopted by clinicians and patients without requiring additional health care infrastructure or affecting patient management.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Skin Cancer

Checkpoint Inhibitors (Nivolumab [Opdivo], Pembrolizumab [Keytruda]) for Treatment of Advanced Melanoma

- **Key Facts:** A medical need exists for novel treatments for advanced melanoma, because despite advances in melanoma therapies, outcomes are poor. Researchers have demonstrated that several types of cancer have developed mechanisms to evade the cellular immune response, in particular the cytotoxic response involving T cells. Under normal conditions, immune cells use these so-called immune checkpoints to prevent exaggerated immune responses, which could damage neighboring tissues and organs. A promising melanoma-treatment approach involves immune-system checkpoint inhibitors, which prolong the patient's immune cytotoxic T-lymphocyte response, targeting and killing cancer cells. Although another drug, ipilimumab, an antibody against the CTLA-4 receptor, has shown durable immune response in some patients, such response is limited to a small number of patients. Additionally, researchers have shown high expression of the PD-1 ligand in cancer cells, a biomarker also involved in suppressing the immune response in patients with melanoma. Researchers are studying the PD-1-specific antibodies nivolumab and pembrolizumab as treatment for advanced melanoma. The drug class is also under study for NSCLC, gastric cancer, blood cancers, and cancers of the breast, head and neck, and urothelial tract.

Nivolumab. Weber and colleagues (2015) presented results from a phase III trial in which patients with ipilimumab-refractory, advanced melanoma had an objective response rate of 32% with nivolumab, which was significantly greater than the response rate in patients receiving chemotherapy. Robert and coworkers (January 2015) reported findings from a second phase III trial that compared nivolumab with dacarbazine in untreated patients with advanced melanoma. Treatment with nivolumab showed an improvement in overall survival and progression-free survival, compared with dacarbazine. Additionally, Larkin and collaborators (2015) published results from a third phase III trial, in which the efficacy and

safety of nivolumab plus ipilimumab was compared with those drugs as monotherapies. Published results showed the combination improved progression-free survival but was also associated with a higher rate of treatment-related adverse events. The most common nivolumab-related adverse events were fatigue, pruritus, and nausea.

Pembrolizumab. In results from a 135-patient, placebo-controlled trial of pembrolizumab, the highest response rate was observed in 52% of patients with advanced melanoma who were treated with 10 mg/kg of the drug every 2 weeks. In this trial, Hamid and colleagues (2013) found no statistical significance in the response rate between patients treated with pembrolizumab who had received prior ipilimumab treatment and those who had not. The most common adverse events associated with pembrolizumab treatment were fatigue, rash, pruritus, and diarrhea and were observed in 79% of patients. Similarly, results from the phase III KEYNOTE-006 trial reported by Robert and coauthors (April 2015) demonstrated that two different regimens of pembrolizumab improved the rates of progression-free survival, and overall survival, as compared with standard treatment with ipilimumab. These observations led an independent data monitoring committee to recommend stopping the trial early.

FDA approved nivolumab in December 2014 under its accelerated approval program for treating patients with advanced melanoma after treatment with ipilimumab or a BRAF inhibitor. In September 2014, FDA approved pembrolizumab for treating ipilimumab-resistant metastatic melanoma under the agency's accelerated approval process; December 18, 2015, FDA granted full approval for treating patients with unresectable or metastatic melanoma and disease progression after ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. At the time of the initial approval, improved survival or disease-related symptoms was not established; however, in accordance with the accelerated approval process, FDA granted full approval upon verification of clinical benefit, which has now been demonstrated in the KEYNOTE-002 and KEYNOTE-006 trials. In December 2015, FDA also approved pembrolizumab as first-line therapy for treating unresectable or metastatic melanoma.

As of September 2015, nivolumab reportedly cost about \$2,500 for a 100 mg vial, while pembrolizumab cost about \$6,600 for three 50 mg vials (it is also available through an expanded-access program). Nivolumab and pembrolizumab are listed on many third-party payers' formularies as specialty pharmaceuticals that require prior authorization.

- **Key Expert Comments:** Nivolumab and pembrolizumab have moderate potential to address an unmet need for melanoma treatment, some experts thought, attributing their assessment to scarce safety and efficacy data and a similar mechanism of action to that of approved and other soon-to-be-approved melanoma therapies. However, other experts regarded nivolumab and pembrolizumab as having high-impact potential to fulfill the unmet need because they can be used as second-line treatment in patients with very poor prognoses whose disease has relapsed after treatment with ipilimumab or BRAF inhibitors. Checkpoint inhibitors are the most important therapeutic breakthrough for treating refractory melanoma, two clinicians strongly argued. Because of the lack of options for this patient population, checkpoint inhibitors are expected to be adopted by both clinicians and patients, thought the experts, who also did not anticipate the drugs would have significant impacts on infrastructure, patient management, or health disparities.
- **High-Impact Potential:** Moderately high

Talimogene Laherparepvec (Imlygic) for Treatment of Advanced Melanoma

- **Key Facts:** Advanced or metastatic melanoma is usually associated with poor patient outcomes. Despite the availability of approved treatment options for these patients, response is limited because of drug resistance developed by cancer cells; thus, an unmet need exists for novel treatments for melanoma. Talimogene laherparepvec (T-VEC; Imlygic™) is a herpes virus bioengineered to no longer express the neurovirulence genes *ICP34.5* and *ICP47*. Deleting these gene expressions allows T-VEC to selectively replicate in cancer cells and increase their antigen presentation, both of which purportedly kill cancer cells without affecting normal cells. Additionally, T-VEC also expresses GM-CSF, a cytokine that helps recruit cells that initiate the immune response against pathogens and cancer cells. In a phase II trial, Kaufman and coworkers (2010) demonstrated that patients treated with T-VEC had more melanoma-specific T cells than did patients treated with GM-CSF alone. Because of its novel mechanism of action, T-VEC could be less likely to lead to drug resistance, which gives it the potential to address this medical need. T-VEC is being tested in the phase III OPTiM/Study as treatment for unresectable stage IIIb, IIIc, or IV melanoma, in which patients are treated per lesion with up to 4 mL (10^6 pfu/mL) of T-VEC; after 3 weeks of rest, patients receive followup doses at a concentration of 10^8 pfu/mL, biweekly. Kaufman and colleagues (2014) reported a significant increase in durable response rates in patients treated with T-VEC compared with such rates in patients who were treated with only GM-CSF. Although overall survival was not statistically significant, it had a favorable trend towards treatment with T-VEC.

The results from this study were the basis for a biologics license application submitted to FDA, which was approved in October 2015 for locally treating cutaneous, subcutaneous, and nodal lesions in patients with previously resected melanoma. Like other oncology drugs, T-VEC is expected to be expensive and third-party payers will likely offer coverage for its FDA-approved indication as a specialty pharmaceutical requiring prior authorization.

- **Key Expert Comments:** Experts commenting on T-VEC are aware of the unmet need for novel interventions to treat patients who have melanoma have exhausted their treatment options. T-VEC is expected to be adopted by clinicians and patients without needing additional infrastructure or affecting patient management; however, because it is an oncolytic virus, some clinicians and patients may have some reservations about adopting T-VEC as a treatment option. As a first-in-class agent, T-VEC has potential to benefit patients whose disease does not respond to standard of care and patients whose disease has managed to evade immune surveillance, two experts opined. Conversely, three experts thought T-VEC will have a limited ability to improve patient outcomes and that only a small percentage of patients with melanoma will have strong responses to treatment. However, two clinicians noted that preliminary clinical data of T-VEC combined with emerging melanoma drugs have shown promising results and, if corroborated, would be a strong indication about the potential of T-VEC to address the unmet need for patients with melanoma.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Breast Cancer Intervention

Palbociclib (Ibrance) for Treatment of Estrogen Receptor–Positive Breast Cancer

Unmet need: The American Cancer Society estimated that in 2015, more than 234,000 cases of invasive breast cancer would be diagnosed in the United States.¹ In 75% of diagnosed breast cancers, tumor cells express high levels of the estrogen receptor, which is called estrogen receptor–positive (ER-positive) disease. Therapeutic alternatives for patients with ER-positive breast cancer are drugs that inhibit ER signaling directly or inhibit the pathway responsible for synthesizing estradiol, the ER ligand. To reduce the chance of drug resistance, oncologists suppress the estrogen-signaling pathway by treating patients with alternating drug regimens. Despite taking such precautions and observing a strong response to treatment, drug resistance still develops and a significant number of patients with ER-positive breast cancer die of the disease.² A need exists for drugs targeting elements downstream of the estrogen-signaling pathway with the potential to reduce the incidence of drug resistance.

Cyclin-dependent kinases (CDKs) 4 and 6 and cyclin D are such downstream elements—they are key proteins in the cell cycle for initiating DNA synthesis.^{3,4} Like other types of cancer, ER-positive breast cancer cells frequently have overactivated CDK 4 and 6 and overexpressed cyclin D. Palbociclib (Ibrance®) purportedly targets and selectively inhibits CDKs 4 and 6 to block cell-cycle progression and inhibit proliferation of tumor cells.^{3,5} Phase III trials are testing palbociclib in several ER-positive breast cancer treatment settings.⁶

Intervention: A hallmark of cancer is excessive cell growth caused by uncontrolled progression through the cell cycle. This growth cycle is a stringently controlled process consisting of several phases (G0, G1, S, G2, and M) during which a cell duplicates its DNA and divides into two daughter cells.^{2,3} To prevent uncontrolled cell proliferation, cells have highly regulated checkpoints that inhibit cell-cycle progression unless conditions for DNA replication and cell division are favorable. Cell-cycle checkpoints are regulated by CDKs paired with cyclins, which drive progression from G1 to S phase and G2 to M phase. A key regulator of the G1-to-S transition is the tumor suppressor protein, retinoblastoma (Rb). Defects in the *RB* gene, which encodes for Rb, causes retinoblastoma in children; *RB* was the first tumor suppressor gene identified. Rb's main role involves binding to the transcription factor E2F and preventing it from activating genes required for DNA replication.^{2,3} Cyclin D interacts with CDK4 and CDK6, forming complexes responsible for initiating the transition from G1 to S phase by phosphorylating Rb, which releases transcription factor E2F and allows genes involved in DNA replication to be transcribed.^{3,7} Therefore, agents targeting the activity of CDK4 and CDK6 have the potential to limit cell-cycle progression.

First-generation CDK inhibitors were nonselective, inhibiting CDK4 and CDK6 as well as other CDKs. They required extended treatment sessions, which increased off-target side effects. In part because of these shortcomings, only one CDK inhibitor, palbociclib, has been approved by the U.S. Food and Drug Administration (FDA). Unlike its predecessors, palbociclib was developed to target the CDK4– and CDK6–cyclin D complexes, blocking the complexes' kinase activity and preventing Rb from becoming phosphorylated.⁷ ER-positive breast cancer cells may be particularly sensitive to CDK 4/6 inhibition.³

In luminal breast cells, progesterone and estrogen drive cell proliferation by binding to progesterone receptor (PR) and ER respectively. In ER-positive breast cancer, the ER receives signals from estrogen that promote tumor growth, although PR may or may not be present. Endocrine therapy is the standard treatment for nonresectable ER-positive breast cancer. It includes interventions that target ER activity (e.g., tamoxifen, fulvestrant, toremifene) or aromatase inhibitors (e.g., exemestane, anastrozole, letrozole) that target estrogen synthesis. Endocrine therapy

has been shown to be an effective treatment for ER-positive breast cancer, with manageable side effects; however, up to 50% of patients with ER-positive breast cancer develop endocrine-therapy resistance.⁸⁻¹⁰

Studies have shown cyclin D is crucial for estrogen-induced cell proliferation, which could explain why the amplified cyclin D gene occurs in 15% to 20% of breast cancers and why cyclin D overexpression is associated with poor clinical outcomes.³ Also, gene-expression profiles have shown that CDK6 overexpression is associated with fulvestrant resistance in breast cancer cells.⁸ Inhibiting this step of the cell cycle by targeting CDKs has the potential of decreasing ER-mediated cell proliferation in breast cancer.

Because of its specificity, palbociclib is well tolerated in patients and can be combined with endocrine therapy to increase efficacy and decrease drug resistance. In clinical trials, palbociclib is administered orally to patients at a dosage of 125 mg, daily, in 28-day cycles with 21 days on treatment and 7 days off.¹¹⁻¹⁴

Clinical trials: Palbociclib is being tested primarily as first-line treatment of locoregionally recurrent or metastatic ER-positive/HER2-negative (human epidermal growth factor receptor 2–negative) breast cancer in combination with letrozole in postmenopausal women.^{11,15} Results from the PALOMA-1 trial, a phase II randomized, open-label, placebo-controlled trial of 165 patients, were presented at the 2014 Association for Cancer Research annual meeting.¹⁶ Patients were treated with palbociclib (125 mg daily, for 3 out of 4 weeks) and letrozole (continuous 2.5 mg daily) or letrozole alone. PALOMA-1 met its primary endpoint of improving progression-free survival as determined by investigator assessment (20.2 months with palbociclib plus letrozole vs. 10.2 months with letrozole alone; hazard ratio [HR], 0.49; $p < 0.0004$). In January 2015, the final analysis of progression-free survival based on the cancer's biomarker status was published. Cohort 1 enrolled patients who had ER-positive/HER2-negative biomarker status while cohort 2 included patients who also had cyclin D1 amplification and loss of protein p16 (*CDKN2A* gene product, which inhibits kinase activity of CDK4 and CDK6). Progression-free survival (PFS) significantly improved in patients who received palbociclib plus letrozole. In cohort 1, PFS was 26.1 months with palbociclib plus letrozole vs. 5.7 months with letrozole alone; HR, 0.299; $p < 0.0001$. In cohort 2, PFS was 18.1 months with palbociclib plus letrozole vs. 11.1 months with letrozole alone; HR, 0.508; $p < 0.0046$.¹⁷ Also, analysis of 61 events suggested an overall survival favoring palbociclib plus letrozole, but it was not statistically significant (37.5 months with palbociclib plus letrozole vs. 33.3 months with letrozole alone; HR, 0.81; $p < 0.2105$).¹⁶

Palbociclib was relatively well tolerated by patients. In the PALOMA-1 trial, grade 3 or 4 adverse events occurred more often with the palbociclib plus letrozole combination than with letrozole alone. The most common grade 3 or 4 adverse events included the following:¹⁷

- Neutropenia (54% in the combination-therapy group vs. 1% in the letrozole-alone group)
- Leukopenia (19% vs. 0%)
- Anemia (6% vs. 1%)
- Diarrhea (4% vs. 1%)
- Dyspnea (4% vs. 1%)
- Fatigue (4% vs. 1%)
- Nausea (2% vs. 1%)
- Thrombocytopenia (2% vs. 0%)
- Arthralgia (1% vs. 3%)
- Back pain (1% vs. 1%)

Palbociclib is also being tested as second-line treatment in combination with fulvestrant, an ER antagonist, in patients who have failed endocrine therapy (PALOMA-3) or in combination with

exemestane, a steroidal aromatase inhibitor, in patients whose disease has progressed after treatment with the nonsteroidal aromatase inhibitor (PEARL).^{13,14} At the 2015 American Society of Clinical Oncology annual meeting, Turner and collaborators presented results from PALOMA-3, a placebo-controlled, parallel-assignment phase III trial of 521 patients with advanced ER-positive/HER2-negative breast cancer who were randomly assigned in a 2:1 ratio to receive palbociclib (125 mg, orally, daily, for 3 weeks out of a 4-week cycle) plus fulvestrant (500 mg, intramuscularly on days 1 and 15 of cycle 1, and then on day 1 of each subsequent 4-week cycle) or placebo plus fulvestrant. Combining palbociclib with fulvestrant improved PFS compared with placebo plus fulvestrant (9.2 vs. 3.8 months; HR, 0.42; $p < 0.001$).¹⁸ In April 2015, the manufacturer announced the PALOMA-3 trial was stopped early because an independent data monitoring committee confirmed a significant PFS improvement in women who were treated with palbociclib plus fulvestrant.¹⁹ The most common grade 3 or 4 adverse events were similar to those observed with palbociclib plus letrozole reported in PALOMA-1 and included the following:¹⁸

- Neutropenia (62.0% with palbociclib plus fulvestrant vs. 0.6% with placebo plus fulvestrant)
- Leukopenia (25.2% vs. 0.6%)
- Anemia (2.6% vs. 1.7%)
- Thrombocytopenia (2.3% vs. 0%)
- Fatigue (2.0% vs. 1.2%)
- Febrile neutropenia (0.6% vs. 0.6%)

Also, palbociclib is being studied as an adjuvant in combination with endocrine therapy in patients who are at risk of breast cancer recurrence after surgical resection (PALLAS, PENELOPE-B).¹²

Manufacturer and regulatory status: Pfizer, Inc. (New York, NY), is developing palbociclib. In February 2015, based on results from the phase II PALOMA-1 trial and granting breakthrough therapy designation, priority review, and an accelerated approval pathway, FDA approved palbociclib for use in combination with letrozole for treating advanced ER-positive/HER2-negative breast cancer in the first-line setting.^{4,20} Also, FDA accepted and granted priority review to a supplemental NDA in December 2015 to expand the use of palbociclib in combination with fulvestrant for treating women with progressive advanced ER-positive/HER2-negative breast cancer after endocrine therapy.²¹

Diffusion and cost: As of May 2015, a monthly supply of palbociclib cost about \$10,200 for 21 capsules of 125 mg.²² Eligible patients who are uninsured or underinsured can receive free palbociclib for up to 12 months through Pfizer's RxPathwaysTM program.²³ The U.S. Centers for Medicare & Medicaid Services (CMS) has not issued a national coverage determination for palbociclib. Thus, coverage decisions are left to the discretion of local Medicare Part D drug plans about whether to place it on formulary. A search of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found several that cover palbociclib for treating ER-positive/HER2-negative breast cancer; it is categorized as a specialty pharmaceutical that requires prior authorization for coverage.²⁴⁻²⁷ Drugs intended to treat patients in whom cancer has been diagnosed are typically covered for their FDA-approved indications. Therefore, once policies for palbociclib are updated, most third-party payers are expected to cover its use for treating ER-positive/HER2-negative breast cancers.

Clinical Pathway at Point of This Intervention

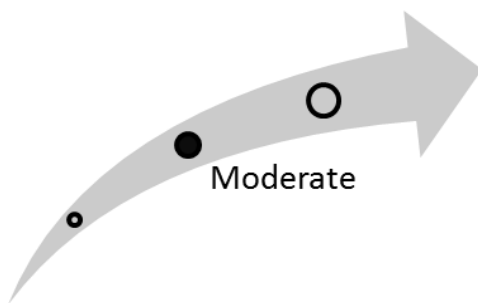
The majority of palbociclib studies are assessing the drug's activity in patients undergoing systemic treatment for locally advanced or metastatic breast cancer. Patients with locally advanced or metastatic ER-positive breast cancer are typically treated with endocrine therapy using aromatase inhibitors or antiestrogens and may undergo multiple rounds of endocrine therapy. Typically patients are first treated with a nonsteroidal aromatase inhibitor (i.e., anastrozole, letrozole). Upon disease progression, patients may be switched to another class of endocrine therapy, often a steroidal aromatase inhibitor (e.g., exemestane) or an ER antagonist (e.g., fulvestrant, tamoxifen). More recently, studies have demonstrated improved outcomes with combination therapy using exemestane and the mammalian target of rapamycin (mTOR) inhibitor everolimus in patients whose disease has progressed after nonsteroidal aromatase inhibitor treatment. Besides endocrine therapies, various cytotoxic chemotherapy regimens may be prescribed; these regimens are typically reserved until patients have tried several endocrine therapies.²⁸ Palbociclib is under study as a complementary or competing intervention to these options in the following trials:

- The PALOMA-1 and PALOMA-2 trials are studying palbociclib in combination with the aromatase inhibitor letrozole in first-line endocrine treatment.
- The PALOMA-3 trial is studying palbociclib in combination with the ER antagonist fulvestrant in patients who have received endocrine therapy.
- The PEARL trial is studying palbociclib in combination with the steroidal aromatase inhibitor exemestane in patients whose disease has become resistant to a nonsteroidal aromatase inhibitor.

Also, endocrine therapy may be used in the adjuvant setting to reduce the risk of breast cancer recurrence in patients who have undergone surgical resection as treatment for localized breast cancer.²⁸ In this setting, palbociclib is being studied in combination with standard endocrine therapy in patients at high risk of breast cancer recurrence (PALLAS and PENELOPE-B trial).

Besides palbociclib, other CDK4/6 inhibitors (e.g., abemaciclib, ribociclib) are under study for treating breast cancer and could eventually compete with palbociclib.⁷

Figure 1. Overall high-impact potential: palbociclib (Ibrance) for treatment of advanced estrogen receptor-positive breast cancer



Patients with metastatic ER-positive breast cancer have access to various types of endocrine therapy. However, in most cases the disease becomes resistant to treatment and progresses, which leaves patients with limited options that lack efficacy. Noting this unmet need, experts commenting on this intervention agreed palbociclib has potential to be an effective option for treating patients after endocrine therapy. Palbociclib targets elements downstream of the estrogen signaling pathway, which reduces the incidence of drug resistance and improves patient outcomes. Although drug-related adverse events are a concern, experts opined patients will accept side effects if the drug extends their survival. The experts noted that broad adoption of palbociclib could be facilitated by its

oral formulation and fact that it targets a novel cell-cycle checkpoint responsible for cancer development. They also thought it is unlikely palbociclib will affect infrastructure, patient management, or health disparities. One expert with research experience noted similar drugs are being investigated, which could also prove to be beneficial to patients. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health technology, and health systems backgrounds, offered perspectives on the topic of palbociclib for treating ER-positive breast cancer.²⁹⁻³⁴ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: ER-positive breast cancer is the most common type of breast cancer. Despite therapies that target ER signaling pathway or inhibit ER ligand synthesis, disease will recur in most patients and it usually does not respond to cytotoxic chemotherapy. Two clinicians and an expert with a health systems perspective concluded a need exists for therapies that target elements downstream of the ER pathway that can prevent recurrence in patients with breast cancer.³²⁻³⁴ Clinical results show palbociclib may benefit patients who fail first-line therapy, an expert thought.³¹ Meanwhile, another expert noted in some breast cancer patients, cyclin D and CDK6 are overexpressed; they are associated with poor outcomes and fulvestrant resistance, respectively. Therefore, palbociclib has potential to improve treatment efficacy while reducing drug resistance.³² Palbociclib is being tested in untreated or minimally treated patients with breast cancer, demonstrating that it has potential to benefit these patients, two clinicians agreed.^{33,34} One of the clinicians also expressed a need for studies assessing safety and efficacy of palbociclib in combination with radiation therapy, chemotherapy, and HER2-specific drugs.³³

Acceptance and adoption: Experts unanimously agreed both physicians and patients will adopt palbociclib because patients have limited alternative treatment options and data show the drug is effective and safe. Although one expert was concerned increased rates of treatment-related leukopenia and neutropenia may deter acceptance, a clinician argued the safety profile is within the range oncologists are used to and they will act accordingly.^{30,34} Similarly, another clinician believes if palbociclib improves outcomes, patients with breast cancer will accept treatment, despite adverse events.³³

Health care delivery infrastructure and patient management: As an orally administered medication, palbociclib would not significantly shift health care staffing or infrastructure, experts anticipated. Also, patient management would not require significant changes; after an oncologist prescribes palbociclib, the patient will continue daily treatments from home and would be monitored frequently for adverse events such as leukopenia and neutropenia.

Health disparities: Palbociclib is unlikely to affect health disparities. Because palbociclib is administered orally, it may be accessible to more patients, in particular those with limited access to infusion centers, an expert argued.²⁹ In contrast, a clinician thought that the high cost of palbociclib, the need for blood draws during the first two cycles, and the treatment regimen could be a barrier for some patients.³³ Although a monthly supply of palbociclib will cost about \$10,000, two experts pointed out a company-sponsored program to offer uninsured and underinsured patients access to palbociclib.^{32,34} An expert with a research perspective thought palbociclib is likely to increase the cost burden in the health care system because it will be an add-on therapy instead of a substitute.³⁰

Colorectal Cancer Intervention

Stool DNA Molecular Test (Cologuard) for Colorectal Cancer Screening

Unmet need: Colorectal cancer (CRC) is the third most common cancer diagnosed in the United States. It tends to develop slowly, and precancerous lesions and early stage CRCs can typically be successfully treated by surgical resection. Successful CRC screening programs could mitigate much of the morbidity and mortality associated with this condition; however, the U.S. Centers for Disease Control and Prevention estimated that in 2012, 34.9% of screening-eligible individuals were not up to date with screening recommendations and 27.7% of screening-eligible individuals had never undergone screening.³⁵ Therefore, new screening methods are highly desired that could increase the percentage of the population that undergoes recommended CRC screening.

Intervention: Cologuard is an in vitro diagnostic test intended to detect genetic signatures of colorectal precancers and cancers in cells shed from the intestinal walls and excreted with stool.³⁶ To undergo screening, patients provide a stool sample of at least 36 g, which is analyzed for the presence of the three following markers associated with CRC and precancerous lesions:

- Hypermethylated DNA derived from two genes known to be methylated in CRCs and adenomas (*NDRG4* and *BMP3*)
- Alleles of the *KRAS* gene known to be acquired as somatic mutations in CRCs and adenomas
- Hemoglobin using a highly sensitive fecal immunoassay

Integrating the methylation marker, mutation marker, and hemoglobin results using a logistic-regression algorithm generates a positive or negative result based on cutoffs established by prior analysis of known samples.³⁷

The test is ordered by the patient's primary care physician or gastroenterologist. According to the manufacturer, the test kit is shipped directly to the patient, who uses it to collect a stool specimen and returns the specimen to the manufacturer's laboratory for processing. Test results are returned to the prescribing physician who, in turn, relays these results to the patient.³⁸

Clinical trials: Cologuard was assessed in a multicenter trial, DEEP-C (n=12,776), comparing the three-component stool DNA test to a commercially available fecal immunochemical test (FIT) alone using colonoscopy as the gold standard. Asymptomatic patients between the ages of 50 and 84 years and considered at average risk of CRC were enrolled in the trial. All patients provided a stool specimen and underwent colonoscopy screening within 90 days of providing the sample. The trial's primary endpoint was the ability of the stool DNA test to detect CRC, with a secondary endpoint of the test's ability to detect advanced precancerous lesions. All stool samples were analyzed in a central laboratory and testers were blinded to results of FIT and clinical findings. Among recruited participants, 9,989 (78.2%) had fully interpretable results, with colonoscopy identifying 65 participants with CRC and 757 participants with advanced precancerous lesions. Compared to FIT, the stool DNA test (including the fecal hemoglobin immunoassay) demonstrated increased sensitivity for CRC (92.3% vs. 73.8%) and precancerous lesions (42.4% vs. 23.8%). Among participants with nonadvanced or negative findings by colonoscopy, the specificity of the stool DNA test and FIT were 86.6% and 94.9%, respectively. In a patient population at average risk for CRC, the number of individuals who would need to be screened to detect one cancer was reported as 154 for colonoscopy, 166 for the stool DNA test, and 208 for FIT.³⁹

Manufacturer and regulatory status: Exact Sciences Corp. (Madison, WI) developed the Cologuard stool DNA screening test. In August 2014, FDA approved the Cologuard test as a CRC screening option.⁴⁰ According to the product labeling, the Cologuard test "is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer (CRC)

or advanced adenoma (AA) and should be followed by diagnostic colonoscopy. Cologuard is indicated to screen adults of either sex, 50 years or older, who are at typical average-risk for CRC. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high risk individuals.”⁴¹

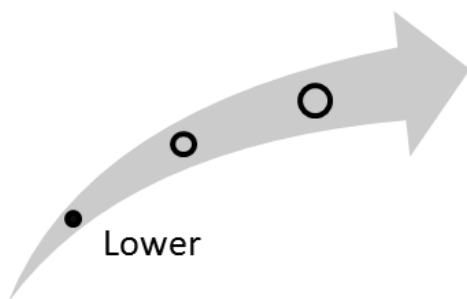
Diffusion and cost: In October 2014, CMS used its new parallel review process for the first time to issue a national coverage determination (NCD) for Cologuard. The process enables CMS coverage review at the same time as FDA regulatory approval review, so the decisions come at about the same time. The NCD indicated that Medicare Part B would cover Cologuard use once every 3 years for beneficiaries who are 50–85 years of age, are asymptomatic for CRC, and are at average risk of developing CRC.⁴² Some third-party payers have begun to extend coverage for Cologuard to non-Medicare patients.⁴³ These coverage determinations are expected to aid the test’s adoption and diffusion, and Exact Sciences reported that 34,000 Cologuard tests were completed in the third quarter of 2015, representing a 60% increase over the previous quarter.⁴⁴ However, the United States Preventive Services Task Force (USPSTF) recently issued draft guidance for its colon cancer screening guidelines, which did not include Cologuard as a recommended screening option, instead listing the test as a screening alternative.⁴⁵ If this status is retained in the final USPSTF guidelines, it could limit future adoption and/or coverage determinations.

Cologuard’s retail price has been reported as \$600 per test.⁴⁶ If used every 3 years, Cologuard would cost about \$1,800 per patient over 9 years. For comparison, annual FIT testing costs about \$25 per test (\$225 every 9 years) and colonoscopy-based screening costs between \$700 and \$3,000 once every 10 years.⁴⁷

Clinical Pathway at Point of This Intervention

Several options are available for routine CRC screening in patients with an average risk of developing CRC, including annual fecal occult blood test (FOBT)/FIT, sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, computed tomography colonography every 5 years, or colonoscopy every 10 years.⁴⁸ For noncolonoscopy tests, positive results require a subsequent colonoscopy to confirm the result and biopsy suspicious polyps.⁴⁸ Multitarget stool DNA testing would provide another CRC screening option that would most likely compete with other noninvasive testing options, such as FOBT/FIT.

Figure 2. Overall high-impact potential: stool DNA molecular test (Cologuard) for colorectal cancer screening



Overall, experts suggested that the large number of screening-eligible patients who are not compliant with screening recommendations and the limited sensitivity of existing noninvasive test methods represent an important unmet need that a novel noninvasive test such as Cologuard could address. However, some commenters questioned the extent to which noncompliant patients would opt for Cologuard-based screening, given the relatively high cost and requirement that patients collect stool samples. Also, experts commenting were divided about the extent to which Cologuard

represents an improvement in detection rates relative to stool tests that detect blood. Therefore, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this topic.⁴⁹⁻⁵⁴ These comments were received in April 2015, before third-party payers began expanding coverage to non-Medicare beneficiaries and before the USPSTF issued its draft guidance. We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The experts suggested that available CRC-screening methods have two shortcomings that Cologuard could potentially address: (1) the reluctance or inability of persons eligible for screening to obtain screening and (2) the low sensitivity of noninvasive methods for detecting CRCs or precancers. The majority of experts commenting suggested that this represents an unmet need that is moderately to very important. However, one commenter speaking from a research perspective suggested that Cologuard represents only a small shift relative to available noninvasive tests based on testing for blood in stool.⁵⁴

In this vein, most experts commenting suggested that Cologuard's potential to improve patient health is only minimal, questioning whether Cologuard's availability would actually improve screening rates and raising caveats about the data from the pivotal clinical trial. For example, one research commenter suggested that it seems unlikely that patients compliant with screening via colonoscopy would transition to Cologuard-based screening and that, if Cologuard were used as a replacement for existing fecal blood tests, its impact would be only incremental.⁵⁴ Also, two research experts noted that the pivotal trial of Cologuard involved only a single episode of screening, and questioned whether the observed improvement in sensitivity with Cologuard would be maintained when tests were used iteratively over the course of several years (i.e., Cologuard once every 3 years vs. FIT annually).^{51,53} Conversely, experts viewing Cologuard's potential to improve patient health more favorably suggested that Cologuard's improved sensitivity relative to FIT and potential to increase screening compliance by expanding the menu of testing options represents an important improvement over current screening methods.^{49,52}

Acceptance and adoption: Experts commenting were divided in their opinions about the acceptance and adoption of Cologuard. In terms of factors promoting clinician adoption, experts commenting cited the ease of ordering the test (i.e., no significant training/infrastructure required),⁵² the desire to improve screening rates,⁵⁰ the availability of insurance coverage,⁴⁹ and the need for improved options for patients who refuse colonoscopy.⁵¹ Conversely, several experts suggested that clinicians would be reluctant to promote Cologuard's adoption, given the availability of other screening options with more established real-world utility. In particular, some experts suggested that clinicians would be highly unlikely to transition patients from colonoscopy to Cologuard. Also, several experts suggested that the substantially higher cost of Cologuard relative to fecal blood tests could dissuade some clinicians and patients from opting for the test. However, it should be noted that experts provided comments before the recent expansion of insurance coverage by some payers to non-Medicare patients, which could limit the impact of this concern. Other factors that experts envisioned as limiting Cologuard adoption included discomfort with collecting stool samples, which could limit compliance with testing in patients prescribed test kits.

Health care delivery infrastructure and patient management: Expert comments on potential changes to health care delivery infrastructure and patient management diverged according to whether the commenter viewed the test as an alternative to colonoscopy or an alternative to other noninvasive test methods. If the multitarget stool DNA test were to replace colonoscopy for some patients, experts suggested, it would cause minimal to moderate shifts in both infrastructure and

patient management. They cited the reduction in demand for screening colonoscopy and a shift of required resources away from endoscopy suites. One clinician commenter noted that a shift from outpatient colonoscopy to stool DNA screening would decrease the burden on patients regarding both bowel preparation and the need for transportation assistance after the sedative typically used during colonoscopies.⁵² On the other hand, if the multitarget stool DNA test were to replace other noninvasive tests, the majority of commenters thought little change would occur in health care infrastructure or patient management, considering that the tests would be used in a highly similar manner to the existing tests (i.e., home sample collection and laboratory analysis). Three experts with research or health systems perspectives suggested that adopting multitarget stool DNA testing among patients who are not compliant with screening recommendations could increase demand for colonoscopy services because of both true-positive and false-positive results.^{49,50,54}

Health disparities: Experts' opinions differed about the effect of Cologuard on health disparities. Several commenters suggested that a better noninvasive test option could improve screening among underserved patient populations that might not have easy access to colonoscopy, potentially decreasing health disparities. However, one expert suggested that the cost of multitarget stool DNA testing relative to existing noninvasive screening tests could further exacerbate existing health disparities if this cost difference restricts its use.

Gastric Cancer Intervention

Ramucirumab (Cyramza) for Treatment of Gastric Cancer

Unmet need: The majority of patients with gastric cancer present with locally advanced or metastatic disease.⁵⁵ Despite recent advancements in surgical techniques, radiotherapy, and chemotherapy, the prognosis for these patients remains poor.⁵⁶ Inhibiting the vascular and epidermal growth factor pathways using targeted drugs has been a focus of experimental therapies for treating gastric cancers, but to date, these therapies have had limited success.^{55,57,58} Ramucirumab (Cyramza®) is a novel, targeted approach to inhibiting angiogenesis (i.e., formation of new blood vessels) via direct interaction with vascular endothelial growth factor receptor 2 (VEGFR2). Through its novel approach to inhibiting angiogenesis, ramucirumab may improve clinical outcomes in patients with advanced gastric cancers.

Intervention: Vascular endothelial growth factors (VEGFs) are highly expressed by many tumor types and are thought to signal to their cognate receptors (e.g., VEGFR2) on endothelial cells, promoting these cells' proliferation, migration, and survival. These processes are essential to blood vessel development, which is thought to be required for both the growth of large tumors and metastasis (i.e., systemic spread) of cancers. Increased VEGF expression in tumors and serum is linked with lymph node involvement, metastasis, and poor outcomes for patients with advanced gastric cancer, providing a rationale for this approach.^{55,59-61}

Existing angiogenesis inhibitors using the VEGF/VEGFR signaling axis target either a single VEGFR ligand (e.g., VEGF-A by bevacizumab) or inhibit multiple receptor tyrosine kinases (e.g., the multikinase inhibitors sorafenib and sunitinib). Because several VEGFs exist in the body, targeting a single VEGF may allow residual VEGFR activation by other ligands. Conversely, because available small-molecule kinase inhibitors simultaneously modulate several signaling pathways, they may have less favorable efficacy or toxicity profiles than agents of greater specificity.

Ramucirumab is a human monoclonal antibody specific for VEGFR2. It binds to the extracellular domain of VEGFR2, blocking this receptor from interacting with any VEGF ligands and inhibiting the downstream signaling cascade.^{62,63} By targeting VEGFR2 and preventing interaction with all VEGFR2 ligands, ramucirumab may exhibit enhanced target inhibition and higher specificity than available VEGF/VEGFR-targeted agents.⁶³ Among VEGFR2-specific agents, ramucirumab is furthest along in development.⁶² It is administered intravenously at a dosage of 8 mg/kg every 2 weeks of a 4-week cycle.⁶⁴

Clinical trials: Ramucirumab has been tested as second-line monotherapy for gastric cancer (REGARD trial)⁶⁵ and as combination therapy with paclitaxel (RAINBOW trial).^{66,67} Also, ramucirumab is being tested in the first-line setting in combination with cisplatin and capecitabine as treatment for patients with gastric cancer whose disease recurs after adjuvant or neoadjuvant systemic therapy (RAINFALL trial).⁶⁸

Results from a phase III, randomized, double-blind, placebo-controlled trial of 355 patients (REGARD) were published in January 2014.⁶⁵ Used as a second-line monotherapy at a dosage of 8 mg/kg every 2 weeks, ramucirumab met its primary endpoint of improving overall survival in patients (5.2 months with ramucirumab vs. 3.8 months with placebo; HR, 0.776; $p=0.042$).⁶⁵

Although the overall survival improvement in the REGARD trial seems incremental, these results have similar survival benefits to those observed in trials comparing second-line cytotoxic chemotherapy to best supportive care. The results from this trial confirm the participation of VEGFR2 in advanced gastric cancer and the importance of targeting this pathway to improve outcomes in this patient population.⁶⁵ As monotherapy, ramucirumab treatment was well tolerated by patients. The drug's prescribing information lists the most common side effects observed in

patients with advanced gastric cancer: hypertension and diarrhea.⁶⁴ In the REGARD trial, the most common grade 3 adverse events experienced by patients were as follows:^{64,65}

- Hypertension (8% ramucirumab vs. 3% placebo)
- Fatigue (6% vs. 10%)
- Anemia (6% vs. 8%)
- Abdominal pain (6% vs. 3%)
- Ascites (4.2% vs. 4.3%)
- Hyponatremia (3.4% vs. 0.9%)
- Decreased appetite (3% vs. 3%)

As a combination therapy, ramucirumab and paclitaxel treatment reportedly met the endpoint of increasing overall survival by 2.27 months (9.63 months with ramucirumab plus paclitaxel vs. 7.36 months with paclitaxel; HR, 0.807; p=0.0169).^{66,67}

Researchers presented the results from a phase III, double-blind RCT of 665 patients (RAINBOW) at the 2014 Gastrointestinal Cancers Symposium. Although median overall survival was 1.6 times higher in the ramucirumab and paclitaxel combination group (RAINBOW) than in the ramucirumab-alone group (REGARD), drug-related toxicities occurred at least twice as often in the combination-therapy group. The most common grade 3 and higher adverse events reported in the RAINBOW trial were as follows:⁶⁶

- Neutropenia (40.7% ramucirumab plus paclitaxel combination vs. 18.8% paclitaxel alone)
- Leukopenia (17.4% vs. 6.7%)
- Hypertension (14.1% vs. 2.4%)
- Anemia (9.2% vs. 10.3%)
- Fatigue (7.0% vs. 4.0%)
- Abdominal pain (5.5% vs. 3.3%)
- Asthenia (5.5% vs. 3.3%)

Manufacturer and regulatory status: Ramucirumab was developed by ImClone Systems, a subsidiary of Eli Lilly and Co. (Indianapolis, IN). Based on the REGARD trial results, Lilly submitted a biologics license application (BLA) to FDA for ramucirumab monotherapy for treating gastric cancer; FDA granted the BLA priority review. It approved ramucirumab in April 2014 for treating advanced gastric cancer or gastroesophageal junction adenocarcinoma, after fluoropyrimidine/platinum-based chemotherapy.⁶⁹ In November 2014, basing its decision on results from the RAINBOW trial, FDA granted ramucirumab a second approval as second-line treatment in combination with paclitaxel for advanced gastric cancer.⁷⁰

The drug is being used in other indications, too. In December 2014, on the basis of the phase III REVEL trial data, FDA approved ramucirumab in combination with docetaxel for treating metastatic nonsmall cell lung cancer (NSCLC) that has progressed after platinum-based chemotherapy. This indication is also intended as treatment for NSCLC caused by genetic alterations in either epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) and that has progressed after targeted therapy.⁷¹ In April 2015, basing its decision on phase III RAISE trial data, FDA approved second-line use of ramucirumab in combination with FOLFIRI for treating patients with metastatic CRC that has progressed after bevacizumab-, oxaliplatin-, and fluoropyrimidine-based chemotherapy.^{72,73}

Diffusion and cost: As of May 2015, ramucirumab reported costs for the biologic were about \$6,300 for six vials of 100 mg/10 mL.⁷⁴ The recommended dose for a typical patient weighing 70 kg is 560 mg (8 mg/kg) per infusion, which is given once every 2 weeks and would cost about \$12,000 for each month of treatment.⁷⁴⁻⁷⁶ For patients who are uninsured or underinsured who are

prescribed an oncology product of Lilly, the Lilly PatientOne program offers reimbursement assistance to eligible patients.⁷⁷

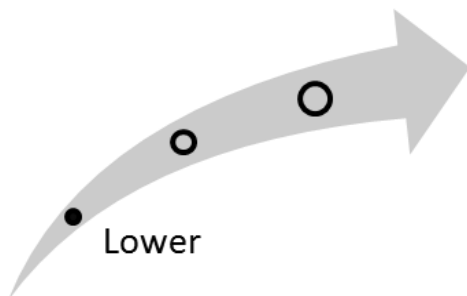
A search of 11 representative, private, third-party payers that publish their coverage policies online found 6 payers with policies covering ramucirumab as medically necessary when prescribed according to FDA-approved indications.⁷⁸⁻⁸³ Other payers may cover the drug by virtue of listing it on their formularies, in the absence of a specific policy. As an intravenous (IV) medication administered in the health care setting, ramucirumab may be covered under Medicare Part B benefits. CMS has assigned an HCPCS Level II code (i.e., C9025) to describe the injection of 5 mg of ramucirumab; this code may be reported several times to describe the administered dose of the drug.⁸⁴

Clinical Pathway at Point of This Intervention

Metastatic gastric cancer is typically treated with systemic chemotherapy.^{58,85} In cases of acute bleeding or gastrointestinal blockage, radiation therapy and/or surgical resection may be employed. First-line chemotherapy typically includes a combination of fluoropyrimidine/platinum-based drugs with or without targeted molecular therapy (e.g., the monoclonal antibody trastuzumab in the case of epidermal growth factor receptor 2 [EGFR2]-positive disease).^{56,58,61} Additional targeted therapies under investigation for treating gastric cancer act on a variety of molecular signaling pathways, including EGFR, hepatocyte growth factor receptor (cMET), mTOR, and VEGF.^{60,61}

In clinical trials for gastric cancer, ramucirumab is administered in combination with paclitaxel or best supportive care as second-line treatment and is likely to be part of combination therapy for metastatic disease that includes other systemic chemotherapies, targeted therapies, or both.⁸⁶

Figure 3. Overall high-impact potential: ramucirumab (Cyramza) for treatment of gastric cancer



Most experts commenting on ramucirumab agreed that a need exists for new therapies for advanced gastric cancer because limited options are available. Although ramucirumab showed efficacy in patients with gastric cancer, some experts thought it has limited potential to fulfill this need because survival was only marginally increased and the benefits might not outweigh the increase in adverse events. However, other experts anticipate as research continues, different treatment combinations that include ramucirumab could potentially have survival benefits longer than those reported in the latest clinical trials. Most experts commenting on ramucirumab agreed that a need exists for new therapies for advanced gastric cancer. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of ramucirumab for treating gastric cancer.⁸⁷⁻⁹² We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Even with advances in surgery, radiation therapy, and chemotherapy, outcomes for patients with gastric cancer are very poor. The experts agreed that an unmet need exists for targeted therapies and that ramucirumab has potential to address this need. However, the experts were concerned about the severe adverse events reported with ramucirumab and chemotherapy as second-line treatment. Three experts pointed out that survival increased by only a few months.^{88,91,92} In contrast, a clinician stated the lack of treatment options would lead patients to tolerate the side effects if it meant extending their lives.⁹²

Acceptance and adoption: Experts anticipate that both physicians and patients will adopt ramucirumab for treating gastric cancer, because of limited second-line alternatives. They thought it would most likely be adopted as combination therapy. Despite the drug's cost and adverse events, patients will probably accept ramucirumab as the only alternative with potential to extend overall survival, two clinicians thought.^{91,92} However, an expert with a health systems perspective remarked that some patients might not consider the potential of an overall survival extension of a couple of months to be worth the added side effects of ramucirumab.⁸⁸

Health care delivery infrastructure and patient management: As an intravenously administered drug, ramucirumab is not expected to change health care delivery and infrastructure and would be easily integrated into clinical care at cancer centers and infusion clinics, noted the experts. Patient management is also expected to remain unaffected. However, one expert anticipated treatment pattern shifts from irinotecan-based therapies to taxane-ramucirumab doublets.⁹¹

Health disparities: Three experts thought that the high cost of ramucirumab could increase disparities, especially for patients with low socioeconomic status who are uninsured or underinsured with high copayments.^{87,89,91} However, another expert pointed out that third-party payers cover use of ramucirumab for gastric cancer; thus, it would not affect disparities.⁹⁰ Even if most expenses are covered by insurance, a clinician stated, ramucirumab is an added cost because about 75% of patients who require second-line treatment receive combination therapy.⁹¹

Hematologic Malignancy Interventions

Blinatumomab (Blincyto) for Treatment of Acute Lymphoblastic Leukemia

Unmet need: Acute lymphoblastic leukemia (ALL) is a heterogeneous collection of aggressive hematologic malignancies arising from cells of the lymphoid lineage. For adult patients in whom ALL has been diagnosed, cure rates using standard treatments are only about 20% to 40%, and survival of patients with recurrent or refractory ALL is only 4.5–6.0 months.⁹³ Therefore, substantial interest exists in novel approaches to treating patients who have ALL.

Intervention: Blinatumomab (Blincyto[®]) is the first to come to market in a new class of immunotherapy drugs known as bi-specific T-cell engagers (BITEs).⁹⁴ BITEs are chimeric antibody constructs that contain binding domains for both a target cell-specific antigen and an immune cell-specific antigen. By binding both antigens simultaneously, the BITE construct purportedly brings the T cells into close proximity with cancer cells, so the T cells potentially can destroy diseased cells. In the case of blinatumomab, the target cell-specific antigen is CD19, a protein expressed by cells of the B-cell lineage, and the immune cell-specific antigen is CD3, a component of the T-cell receptor complex expressed by mature T cells. CD19 is expressed only by the ALL subtype arising from the B-cell lineage; therefore, only this form of ALL is eligible for blinatumomab treatment.⁹⁵

In the bloodstream, blinatumomab has a short half-life; therefore, the drug is given by continuous IV infusion. Patients typically receive blinatumomab in 6-week cycles consisting of 4 weeks of continuous infusion followed by 2 weeks off treatment. After a loading dose of 9 mcg per day for week 1 of the first treatment cycle, patients receive blinatumomab at a dosage of 28 mcg/day.⁹⁵

Clinical trials: The main trial supporting FDA approval of blinatumomab was an open-label, single-arm study with a primary endpoint of the rate of complete response (CR) or complete response with partial hematologic recovery (CRh) within first 2 treatment cycles.⁹⁶ In this trial, 185 adult patients with recurrent/refractory, Philadelphia chromosome-negative ALL received blinatumomab treatment, and the primary endpoint was met in 43% of these patients (33% CR and 10% CRh).

More recently, investigators reported data from a second single-arm trial of blinatumomab in patients with recurrent/refractory, Philadelphia chromosome-positive ALL. Among 45 patients enrolled in this trial, 16 (36%) achieved a CR/CRh (31% CR, 4% CRh) within the first 2 treatment cycles.⁹⁷

The most common adverse reactions reported in patients treated with the drug were pyrexia (fever), headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, tremor, rash, and constipation.⁹⁵ Additionally, the prescribing information includes a black box warning about the potential for 2 potentially life-threatening adverse events: cytokine release syndrome and neurological toxicities, which occurred in 2% and 11% of patients, respectively.^{95,96} These severe adverse events typically occurred within the first week of blinatumomab administration; the prescribing information recommends that patients be hospitalized for the first 9 days of treatment cycle 1 and the first 2 days of treatment cycle 2.⁹⁵

Manufacturer and regulatory status: Blinatumomab was developed by Amgen, Inc. (Thousand Oaks, CA). In December 2014, FDA approved blinatumomab under the agency's accelerated approval pathway for treating Philadelphia chromosome-negative, recurrent or refractory B-cell precursor ALL.⁹⁴ Blinatumomab's biologics license application (BLA) had been granted priority review by the agency, and the accelerated approval came 5 months ahead of the specified decision date.⁹⁴ Before the approval, FDA had granted blinatumomab orphan drug and breakthrough therapy designations.^{98,99} The accelerated approval requires that the potential clinical

benefit of blinatumomab be confirmed in a larger trial, and a confirmatory phase III trial (the TOWER trial) is ongoing.¹⁰⁰ Also, FDA required that a Risk Evaluation and Mitigation Strategy (REMS) program be instituted for blinatumomab to inform health care workers of the potential for severe adverse events (i.e., cytokine release syndrome and neurological toxicities).¹⁰¹

Diffusion and cost: In December 2014, Amgen announced that blinatumomab would be priced at \$89,000 per 4-week cycle.¹⁰² In the phase II trial supporting FDA approval in the recurrent/refractory setting, patients received a median of 2 treatment cycles (range 1–5).⁹⁵ Therefore, drug costs associated with a typical patient receiving blinatumomab would be approximately \$178,000. More recent analyses have suggested that the typical course of treatment may be shorter for the majority of patients, potentially reducing cost of the treatment course.¹⁰³ Additional costs associated with blinatumomab treatment would include administration costs associated with the 24-hour continuous infusion and costs for hospital stays during the first days of treatment cycles 1 and 2.⁹⁵

Our searches of 11 representative, private, third-party payers that publish their coverage policies online identified 4 policies (Horizon Blue Cross Blue Shield NJ, Blue Cross Blue Shield of Tennessee, HealthPartners, Regence) for blinatumomab, which indicated that blinatumomab was covered for its FDA-approved indication.¹⁰⁴⁻¹⁰⁷ CMS had initially indicated that it would not cover the cost of blinatumomab; however, in August 2015, it reversed this decision, implementing a new technology add-on payment to offset the cost of the drug's use by health care facilities.¹⁰⁸

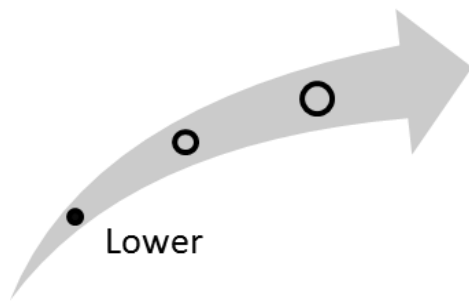
Clinical Pathway at Point of This Intervention

Treatment of patients who have ALL is highly personalized and varies according to each patient's characteristics, goals of therapy, duration of any prior remission, and type of previous ALL treatment. In broad terms, an episode of ALL treatment consists of a series of treatments referred to as follows:

- Induction, intended to induce a remission (i.e., deplete leukemic cells and restore normal hematopoiesis)
- Consolidation/intensification, to eliminate any remaining leukemic cells
- Maintenance, to prevent disease recurrence

In the recurrent/refractory setting, no standard of care exists;¹⁰⁹ however, patients with Philadelphia chromosome–negative, B-cell ALL may undergo induction therapy with multidrug regimens such as augmented hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), clofarabine-containing regimens, cytarabine-containing regimens, or alkylator combination regimens. Alternatively, patients may undergo monotherapy with vincristine sulfate liposome injection.⁹³ For adult patients with recurrent/refractory disease, allogeneic stem cell transplant is the only treatment that has demonstrated the potential to induce long-term remissions and, therefore, patients whose disease responds to induction therapy may be bridged to stem cell transplant in the consolidation/intensification phase of treatment.¹⁰⁹ The recent FDA approval of blinatumomab provides another induction treatment for patients with recurrent/refractory ALL.

Figure 4. Overall high-impact potential: blinatumomab (Blincyto) for treatment of acute lymphoblastic leukemia



Experts commenting on this intervention indicated that available treatments for ALL have significant shortcomings, representing a substantial unmet need. Also, given this need for novel treatments and the promising responses seen in initial trials of blinatumomab, the experts indicated that blinatumomab is likely to be adopted widely by patients and physicians alike. However, experts also cautioned that RCTs of blinatumomab are needed to confirm the clinical benefit. As a drug likely to be given in a standard ALL treatment setting to a small number of patients, blinatumomab was not seen by experts commenting as causing significant shifts in health care infrastructure or patient management. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this topic.¹¹⁰⁻¹¹⁵ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need for more effective treatments in adult patients with recurrent/refractory ALL was seen as substantial by the majority of experts commenting, citing the poor prognosis of patients with available treatment options. Experts commenting suggested a substantial unmet need and also noted the lack of noncytotoxic chemotherapies in this patient population and suggested that blinatumomab's immune-based mechanism of action offers a potentially important alternative. However, multiple commenters also noted that the magnitude of the unmet need blinatumomab could address is limited by the small number of adult patients in whom B-cell precursor, Philadelphia chromosome–negative ALL is diagnosed each year.

Blinatumomab's potential to improve patient health was also viewed favorably by the majority of experts commenting, who cited the promising response rates observed in completed single-arm studies. Two clinical commenters also thought the available data suggested that blinatumomab improved patient survival relative to historical controls.^{114,115} However, several commenters noted that the results observed in single-arm trials of blinatumomab need to be confirmed in randomized trials. Additionally, several commenters noted the significant toxicity associated with blinatumomab treatment. One such commenter, who had a research perspective, suggested that the high rate of adverse events leaves blinatumomab with only minimal potential to improve patient health.¹¹² A clinical commenter suggested that the rates and consequences of these adverse events would need to be carefully monitored in larger studies.¹¹⁴

Acceptance and adoption: Blinatumomab is likely to be moderately to widely adopted by both patients and physicians, according to the majority of commenters. Factors driving acceptance mentioned by several commenters included the limited treatment options for adults with ALL and the promising response rates observed in single-arm trials of blinatumomab. Also, two clinical

commenters suggested that the ease with which blinatumomab could be incorporated into treatment protocols would promote its adoption.^{114,115} Although the majority of commenters suggested that blinatumomab adoption would be strong, several cautioned that the high rate and serious nature of some adverse events could dissuade some clinicians and patients from adopting the drug. One expert with a clinical perspective suggested that this would require careful patient selection for blinatumomab treatment.¹¹⁴ One commenter with a research perspective suggested that the high rate of adverse events would lead to only minimal uptake of the drug by clinicians and patients.¹¹²

Health care delivery infrastructure and patient management: Blinatumomab would have only modest effects on health care delivery infrastructure and patient management, according to the experts commenting. Potentially burdensome aspects of blinatumomab's administration include the requirement for hospitalization during the first days of treatment and the need to monitor patients for severe adverse events as listed in the REMS. However, commenters suggested that these represent small shifts because clinicians who would use blinatumomab for treating acutely ill leukemia patients are familiar with aggressive drug regimens and because of the relatively small number of patients who would be expected to receive blinatumomab treatment.

Health disparities: Blinatumomab has little to no potential to address health disparities according to experts commenting. However, several commenters noted that the high cost of the treatment could widen any existing disparities based on socioeconomic means or access to health insurance.

Ibrutinib (Imbruvica) and Idelalisib (Zydelig) for Treatment of Non-Hodgkin's Lymphomas

Unmet need: Non-Hodgkin's lymphoma (NHL) comprises a set of malignancies that arise from lymphocytes of the immune system. NHLs can derive from either B cells or T cells; however, the majority are of B-cell origin. Treatment of B-cell NHLs has improved in recent years by optimizing chemotherapy regimens and introducing the CD20 antibody rituximab. However, many patients with NHL experience disease recurrence, particularly patients with certain NHL subtypes such as chronic lymphocytic leukemia (CLL) and mantle cell lymphoma. For patients with these conditions whose disease has recurred and resists rituximab, few treatment options exist. Moreover, patients with some forms of CLL, such as CLL harboring a deletion on the short arm of chromosome 17, have a poor prognosis.

Intervention: Ibrutinib (Imbruvica®) is a first-in-class, orally administered, small molecule drug that inhibits Bruton's tyrosine kinase (BTK), a nonreceptor tyrosine kinase that plays several roles in regulating B lymphocytes. Proliferation and survival of malignant B cells may be driven by chronic signaling through the B-cell receptor pathway, which activates several molecular pathways regulating these processes (e.g., AKT, extracellular signal-regulated kinase, NF-kappaB). BTK is essential for the B-cell receptor-mediated activation of these pathways; therefore, inhibiting BTK may inactivate these pathways, potentially depriving malignant B cells of signals driving proliferation and survival.¹¹⁶ Besides BTK's role in regulating proliferation and survival downstream of the B-cell receptor, it may also regulate the trafficking and retention of malignant B cells in the lymph nodes. Lymph nodes may be privileged sites within the body that play a role in the pathogenesis of B-cell malignancies. BTK has been shown to regulate both integrin-mediated adhesion downstream of the B-cell receptor and chemokine-mediated trafficking downstream of various chemokine receptors. Inhibiting BTK with ibrutinib results in an egress of malignant B cells from the lymph nodes into the peripheral blood, which is thought to be caused by inhibiting these pathways.^{117,118}

Idelalisib (Zydelig®) is a first-in-class, orally administered, small-molecule inhibitor of phosphoinositide 3-kinase (PI3K) delta.^{119,120} PI3K plays a central role in regulating fundamental processes such as cell growth, proliferation, and survival. In certain cancers, including NHLs, the PI3K pathway becomes highly active and is thought to contribute to malignant transformation. Like BTK, PI3K signals downstream of the B-cell receptor, and investigators hypothesize that it plays a role in malignant transformation caused by chronic B-cell receptor signaling.¹¹⁶ Four PI3K catalytic subunit isoforms exist: alpha, beta, gamma, and delta. The delta isoform is predominantly expressed in immune-system cells, particularly leukocytes, and is thought to play a role in regulating leukocyte proliferation. Idelalisib is selective for the PI3K delta isoform; therefore, its PI3K pathway inhibition may be limited to hematologic cells, potentially targeting malignant B cells while limiting systemic toxicity that might be associated with pan-PI3K inhibition.^{121,122}

Clinical trials: Investigators have reported results from several trials of ibrutinib and idelalisib for treating various NHLs.

Ibrutinib. From a single-arm, open-label trial (n=85) of ibrutinib (420 or 840 mg, once daily) in patients with CLL who had undergone at least 2 treatments, Byrd and colleagues (2013) reported an overall response rate (as defined by the International Workshop on Chronic Lymphocytic Leukemia [IWCLL] criteria) of 71%. As noted above, ibrutinib's mechanism of action may lead to egress of B cells from the lymph nodes, leading to an increase in absolute lymphocyte count (i.e., lymphocytosis) in a substantial subset of patients. An additional 18% of patients met all IWCLL criteria for partial response except for the absolute lymphocyte count.¹²³

In a separate single-arm, open-label trial of ibrutinib (420 mg, once daily) in 53 patients with high-risk CLL (risk factors: chromosome 17p deletion [n=29], aged 65 years or older [n=24]), Farooqui and colleagues reported an overall response rate of 66%, with an additional 28% of patients exhibiting partial response with lymphocytosis.¹²⁴ Importantly, both ibrutinib trials in patients with CLL demonstrated equivalent response rates in patients with or without a chromosome 17p deletion.^{123,124}

More recently, researchers presented results from the RESONATE, HELIOS, and RESONATE-2 randomized controlled trials of ibrutinib in patients with CLL. The open-label RESONATE trial enrolled 2 groups of patients who were poor candidates for purine analog therapy: (1) patients with either CLL or small lymphocytic lymphoma who had a short duration of response to chemoimmunotherapy and (2) patients with coexisting illnesses, an age of 70 years or more, or a chromosome 17p deletion. Patients (n=391) were randomly assigned to receive either ibrutinib (420 mg, once daily) or ofatumumab (300 mg initial dose, 2,000 mg weekly for weeks 2–8, and 2,000 mg every 4 weeks for weeks 12–24). Patients receiving ibrutinib exhibited improved progression-free survival, compared with patients receiving ofatumumab (median not reached vs. 8.1 months; HR, 0.215; $p<0.0001$) and improved overall survival (median not reached in either arm; HR, 0.434; $p=0.005$).¹²⁵ Investigators noted that the progression-free survival benefit observed for ibrutinib was maintained in the subgroup of patients with a chromosome 17p deletion (median not reached vs. 5.8 months; HR, 0.25; 95% confidence interval [CI], 0.14 to 0.45).¹²⁶

The double-blind HELIOS trial enrolled patients with recurrent/refractory CLL or small lymphocytic leukemia who had undergone at least one chemotherapy regimen. Patients were randomly assigned to receive either standard therapy consisting of bendamustine and rituximab (BR) plus placebo or BR plus ibrutinib (420 mg once daily). Patients receiving BR plus ibrutinib demonstrated a statistically significant improvement in the primary endpoint of progression-free survival, compared with patients receiving BR plus placebo (median not reached vs. 13.3 months, HR, 0.203; 95% CI, 0.150 to 0.276; $p<0.0001$). This progression-free survival result was obtained at an interim analysis (median followup 17.2 months); because of the observed results, the trial was unblinded and patients in the BR plus placebo arm with confirmed progressive disease were allowed to cross over to ibrutinib treatment.¹²⁷

The open-label RESONATE-2 trial enrolled patients aged 65 years or older with treatment-naïve CLL or small lymphocytic leukemia. Patients were randomly assigned to receive treatment with chlorambucil or ibrutinib (420 mg once daily). Patients receiving ibrutinib demonstrated a statistically significant improvement in the primary endpoint of progression free survival, compared with patients receiving chlorambucil (median not reached vs. 18.9 months, HR, 0.16; 95% CI, 0.09 to 0.28, $p<0.0001$).¹²⁸

For patients with Waldenström's macroglobulinemia, data are available from a single-arm, open-label trial of ibrutinib monotherapy (420 mg, once daily) in 63 patients who had received at least 1 prior treatment. Treon and colleagues reported an overall response rate of 90.5% (including a major response rate of 73%). Also, investigators reported rates of progression-free and overall survival at 2 years of 69.1% and 95.2%, respectively.¹²⁹

In clinical trials, ibrutinib was reported as being well tolerated, with the majority of adverse events being of mild-to-moderate severity.^{123,124,126,128,129} Additionally, data from the HELIOS trial combining ibrutinib with bendamustine and rituximab reported an adverse profile consistent with the known toxicity of the individual drugs.¹²⁷ According to ibrutinib's prescribing information, common adverse events included thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, bruising, nausea, upper respiratory tract infection, and rash. Also, the prescribing information contains warnings and precautions regarding the potential for hemorrhage,

infections, atrial fibrillation, second primary malignancies, tumor lysis syndrome in patients with high tumor burden, and embryo-fetal toxicity.¹³⁰

Idelalisib. Regarding idelalisib, investigators published results in 2014 from a randomized, double-blind, placebo-controlled trial of patients with recurrent/refractory CLL.¹³¹ In this trial, 220 patients with decreased renal function, previous therapy-induced myelosuppression, or major coexisting illnesses received rituximab and either idelalisib (150 mg twice daily) or matching placebo. On the primary endpoint of progression-free survival, the median progression-free survival had not been reached at the time of analysis in the idelalisib group; a median progression-free survival of 5.5 months was reported in the placebo group (HR for progression or death, 0.15; $p < 0.001$). Overall response rate also favored patients in the idelalisib arm compared with patients in the placebo arm (81% vs. 13%; odds ratio, 29.92; $p < 0.001$). Serious adverse events occurred in 40% of patients in the idelalisib arm compared with 35% of patients in the placebo arm.

More recently, investigators presented results from two additional randomized controlled trials in patients with recurrent CLL.^{132,133} In study 119, 261 patients with recurrent CLL were randomly assigned in a 2:1 ratio to receive either idelalisib (150 mg twice daily) plus ofatumumab or placebo plus ofatumumab. Combining idelalisib with ofatumumab demonstrated a significant improvement in the primary endpoint of progression-free survival compared with such survival under ofatumumab alone (16.3 vs. 8.0 months; HR, 0.27; $p < 0.0001$). The overall response rate also favored the combination arm (75.3% vs. 18.4%; odds ratio, 15.9; $p < 0.0001$). Investigators reported that toxicity of the idelalisib-containing regimen was manageable and similar in profile to previous reports.¹³²

In Study 115, 416 patients with recurrent/refractory CLL were randomly assigned to receive either BR plus idelalisib or BR plus placebo. At an interim analysis, the idelalisib arm demonstrated a significant improvement in the primary endpoint of progression-free survival compared with the placebo arm (23 vs. 11 months; HR, 0.33, $p = 2.8 \times 10^{-14}$). After this interim analysis, the independent data monitoring committee recommended unblinding of the trial based on the “overwhelming efficacy” of the idelalisib-containing regimen.¹³³

Investigators also published results from a trial of idelalisib in patients with recurrent/refractory indolent NHL (follicular lymphoma, small lymphocytic lymphoma, marginal-zone lymphoma, or lymphoplasmacytic lymphoma) who had received between 2 and 12 previous indolent NHL therapies (median 4).¹³⁴ In this trial ($n = 125$), all patients received idelalisib (150 mg twice daily). Investigators reported a 57% response rate, including a 6% complete response rate.

In clinical trials, treatment with idelalisib was reported as being well tolerated, with the majority of adverse events being mild to moderate in severity.^{131,134} Frequent adverse events associated with idelalisib monotherapy included cough, diarrhea, dyspnea, fatigue, fever, pneumonia, and rash.¹³⁴ Frequent adverse events associated with idelalisib used in combination with rituximab included chills, cough, fatigue, infusion-related reactions (due to rituximab infusion), nausea, and fever. Rates of chills, diarrhea, fever, and rash were higher in the idelalisib plus rituximab arm than in the placebo plus rituximab arm.¹³¹ Idelalisib’s prescribing information carries a black box warning regarding the potential for the following fatal and/or serious toxicities: hepatotoxicity, diarrhea or colitis, pneumonitis, and intestinal perforation.¹³⁵

Manufacturer and regulatory status: Ibrutinib. Ibrutinib was developed by Pharmacyclics, Inc. (Sunnyvale, CA), in collaboration with the Janssen Biotech unit of Johnson & Johnson (New Brunswick, NJ). In May 2015, AbbVie (North Chicago, IL) acquired Pharmacyclics, which will be a wholly owned subsidiary of AbbVie.¹³⁶

The first FDA approval for ibrutinib came in November 2013 for treating patients with mantle cell lymphoma, a topic that was retired from the AHRQ horizon scanning system after being

tracked for 2 years after approval.¹³⁷ Subsequently, in February 2014, FDA granted ibrutinib second accelerated approval for treating CLL in patients who have received at least one prior therapy.¹³⁸ In July 2014, FDA converted the accelerated approval of ibrutinib for treating relapsed/refractory CLL to a full approval, indicating that data from the phase III RESONATE trial “confirmed the drug’s clinical benefit.” Additionally, the FDA-approved indication for CLL was expanded to include a set of high-risk patients whose disease harbors a deletion on chromosome 17.¹³⁹ Lastly, in January 2015, FDA expanded ibrutinib’s list of approved indications to include patients with Waldenström’s macroglobulinemia.¹³⁰ Before these approvals, FDA had granted ibrutinib breakthrough therapy status for three indications: (1) CLL harboring a chromosome 17 deletion, (2) recurrent/refractory mantle cell lymphoma, and (3) Waldenström’s macroglobulinemia.¹⁴⁰

Idelalisib. Idelalisib was developed by Gilead Sciences, Inc. (Foster City, CA). In July 2014, FDA approved idelalisib for three types of recurrent/refractory NHL: CLL, small lymphocytic lymphoma, and follicular lymphoma.¹⁴¹ Before these approvals, FDA had granted idelalisib breakthrough therapy status for treating patients with CLL.¹⁴²

Both ibrutinib and idelalisib are under study in a wide range of clinical trials that could lead to expansion of the range of NHLs and/or NHL treatment settings approved by FDA. AbbVie has indicated that it has submitted supplemental new drug applications (sNDAs) to FDA for (1) ibrutinib monotherapy in treatment-naïve patients with CLL based on the results of the RESONATE-2 trial and (2) ibrutinib in combination with bendamustine and rituximab in previously treated patients with CLL, based on the results of the HELIOS trial.^{143,144} Gilead has submitted an sNDA for using idelalisib in combination with ofatumumab in previously treated patients with CLL, based on the results of Study 119. The company intends to submit an sNDA for using idelalisib in combination with bendamustine and rituximab in previously treated patients with CLL, based on the results of Study 115.^{145,146}

Diffusion and cost: As of November 2015, the average retail price for 1 month of ibrutinib at the recommended dose for CLL or Waldenström’s macroglobulinemia (420 mg, once daily) was reportedly \$9,879.¹⁴⁷ Patients take the drug until disease progression or unacceptable toxicity. In clinical trials for treating CLL, patients received ibrutinib treatment for a median of about 9 months;¹²⁶ however, many patients were still taking ibrutinib at the cutoff for data analysis, and the real-world duration of treatment has not been established. In the phase II clinical trial in treating Waldenström’s macroglobulinemia, patients received treatment for a median of about 19 months and 68% of patients were still receiving treatment at the time of the analysis.

A 1-month supply of idelalisib (sixty 150-mg idelalisib tablets) was reportedly \$8,173 as of November 2015.¹⁴⁸ For treating patients with CLL, idelalisib is approved only as a combination therapy with the anti-CD20 monoclonal antibody rituximab. Combination therapy with idelalisib and rituximab could cost closer to \$12,000 per month, with rituximab administered during the first 5 months of treatment.^{135,149}

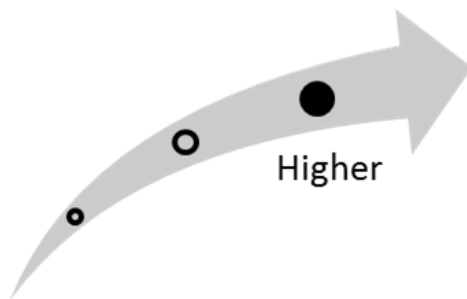
Our searches of 11 representative, private, third-party payers that publish their policies online found most have policies regarding ibrutinib and idelalisib that cover the drugs according to labeled indications when certain conditions are met.¹⁵⁰⁻¹⁵⁷ These drugs are considered specialty pharmaceuticals that require prior authorization for coverage.

Clinical Pathway at Point of This Intervention

Treatment of B-cell NHLs is highly individualized, based on the subtype of NHL diagnosed in the patient, the patient’s overall condition, and his or her response to any earlier lines of therapy. Treatments for CLL, indolent NHL, and mantle cell lymphoma include various combinations of cytotoxic agents, typically in combination with the monoclonal antibody rituximab. Other agents

used in treating recurrent/refractory NHLs include alemtuzumab, lenalidomide, obinutuzumab, and ofatumumab for CLL and alemtuzumab, bortezomib, everolimus, ofatumumab, and thalidomide for Waldenström's macroglobulinemia.^{158,159} Ibrutinib and idelalisib would represent additional treatment options for patients with recurrent B-cell NHL or certain patients with previously untreated NHL subtypes associated with poorer outcomes (e.g., patients with CLL harboring a chromosome 17p deletion).

Figure 5. Overall high-impact potential: ibrutinib (Imbruvica) and idelalisib (Zydelig) for treating non-Hodgkin's lymphomas



Overall, experts commenting on these interventions thought that a significant need exists for novel treatments of B-cell lymphomas and that the response rates observed in initial trials of ibrutinib and idelalisib indicated that the drugs have significant potential to improve patient outcomes. However, experts suggested that further study is needed to confirm this early promise, particularly studies comparing ibrutinib and idelalisib to alternative treatments. Experts thought that the relatively benign side-effect profile of these two drugs and their potential to be used for extended periods of time to treat several B-cell malignancies are significant. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Ibrutinib

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of ibrutinib for treating CLL,¹⁶⁰⁻¹⁶⁵ and six experts, with similar backgrounds, offered perspectives on the topic of ibrutinib for treating Waldenström's macroglobulinemia.¹⁶⁶⁻¹⁷¹ One commenter with a research perspective offered perspectives on both topics.^{161,168} We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Most experts commenting cited a moderate to high unmet need for new treatments for CLL and Waldenström's macroglobulinemia. However, several commenters noted that the relatively small number of patients affected by the diseases (particularly Waldenström's macroglobulinemia) limits the magnitude of the unmet need generally. For CLL, experts cited the propensity of these malignancies to recur and the lack of effective treatment options and for older patients unable to tolerate intensive chemotherapy regimens. With regard to Waldenström's macroglobulinemia, experts noted the lack of FDA-approved treatment options for patients with the disease. Two experts with research and clinical perspectives who indicated the unmet need was only of minimal to moderate importance cited the fact that many off-label treatments are available.^{169,170} However, another clinical expert noted that despite the availability of these treatments, up to half of affected patients die of the disease.¹⁷¹

Ibrutinib's potential to improve health was also considered moderate to high by commenters. For CLL, commenters cited the large number of trials that had demonstrated clinical activity of ibrutinib in this disease. However, several commenters also noted that further study is needed to determine long-term treatment outcomes and to compare outcomes for ibrutinib with those for the variety of treatments currently used to treat the disease. With regards to Waldenström's macroglobulinemia, commenters noted the high response rates reported from phase II trials and the relatively tolerable adverse event profile of the treatment.

Acceptance and adoption: Both clinicians and patients were seen by commenters as highly likely to adopt the use of ibrutinib. Factors encouraging adoption include the limited treatment options for patients with recurrent disease, ibrutinib's encouraging signs of efficacy and limited toxicity, and its ease of administration. However, several commenters suggested that the cost of ibrutinib might be unaffordable for some patients, and thus unadoptable.

Health system infrastructure and staffing: Ibrutinib is orally administered; therefore, most experts did not see its adoption as having a substantial impact on health care staffing or infrastructure. Some potential for change was envisioned if patients who might have received cytotoxic chemotherapy administered by infusion were instead treated with ibrutinib. Commenters noted that this would cause a shift in care setting and suggested that the mild side-effect profile observed thus far for ibrutinib could lessen the demand on health care providers to manage adverse events.

Health disparities: Commenters noted that disparities could be exacerbated for those unable to pay for the drug, because it is costly. One expert with a clinical perspective highlighted the issue of cost for patients with Waldenström's macroglobulinemia, citing the relatively long survival of this patient population and the potential that they could be taking a drug such as ibrutinib for an extended period.¹⁷¹ Cost-driven increases in health disparities would be primarily an issue for the uninsured and those with high copayments, because third-party payers generally cover use of the drug for its FDA-approved indications.

Idelalisib

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of idelalisib for treating CLL,¹⁷²⁻¹⁷⁷ and six experts, with similar backgrounds, offered perspectives on idelalisib for treating indolent NHL.¹⁷⁸⁻¹⁸³ Five experts commented on both topics.^{172,173,175-179,181-183}

Unmet need and health outcomes: The majority of experts thought a moderate unmet need exists for better CLL and indolent NHL treatment; they cited the fact that treatments for these conditions are rarely curative and that options for patients with recurrent/refractory disease have limited efficacy. One clinical expert suggested that patients in whom intensive chemotherapy may be contraindicated (e.g., elderly patients, patients with coexisting conditions) have very limited treatment options.¹⁷³

Idelalisib has moderate potential to improve health in patients with CLL or indolent NHL, according to the majority of experts commenting, who cited the promising data from initial trials and the mechanism of action. However, several commenters cited the preliminary nature of the data and that this left them unsure of the ultimate potential clinical benefit of the drug.^{176,177,183} One expert with a clinical perspective noted that adverse events (in particular colitis) could limit the duration of therapy. This commenter noted that this could complicate expansion of idelalisib use into the first-line setting.¹⁷³

Acceptance and adoption: Both physicians and patients would likely adopt idelalisib, the experts thought, given limited treatment options, ease of oral administration, and preliminary

promising data on efficacy. Experts who envisioned less widespread adoption again cited the preliminary nature of the data and suggested that some physicians and patients would want to await further data before opting for idelalisib. Additionally, experts envisioned that idelalisib's high cost could place a financial burden on patients and cause them to not use it or seek other options.

Health system infrastructure and staffing: As an orally administered drug, idelalisib is unlikely to change health care system infrastructure and staffing, according to the experts. A few suggested that displacing certain intravenously administered CLL and indolent NHL treatments by using idelalisib could shift patient care out of infusion centers; however, this was seen by most commenters as only a minor disruption to the health care system. Additionally, one clinical expert noted that introducing drugs such as idelalisib that are taken on an ongoing basis would cause a shift in patient management from episodic short-term therapy intended to induce temporary remissions to treatment of extended duration intended to manage the disease more like a chronic condition.¹⁷³

Health disparities: Commenters noted that disparities could be exacerbated for those unable to pay for the drug, because it is likely to be costly and copayments may be high. In particular, multiple commenters noted that idelalisib could be taken on an ongoing basis by many patients, which could further increase costs relative to other CLL/indolent NHL treatments.

Monoclonal Antibodies (Daratumumab [Darzalex], Elotuzumab [Empliciti]) for Treatment of Multiple Myeloma

Unmet need: The availability of immunomodulatory drugs (i.e., lenalidomide, pomalidomide, thalidomide) and proteasome inhibitors (i.e., bortezomib, carfilzomib) has improved outcomes in patients with multiple myeloma; however, it remains incurable for the majority of patients.¹⁸⁴ Median survival is only about 5 years, and 11,000 people die of the disease each year in the United States.^{185,186} An unmet need remains for novel treatments with the potential to improve outcomes for patients with multiple myeloma.

Intervention: Daratumumab (Darzalex[®]) and elotuzumab (Empliciti[™]) are two monoclonal antibodies with novel mechanisms of action that FDA recently approved for treating multiple myeloma.^{187,188}

Daratumumab is a human, immunoglobulin G1 monoclonal antibody specific for CD38, a transmembrane protein that researchers have observed to be expressed at high levels on myeloma cells.¹⁸⁹ Investigators have attributed daratumumab's anti-multiple myeloma activity to multiple mechanisms of action. Most notably, daratumumab binding to CD38 on the surface of target cells is thought to induce target-cell death through two activities of the innate immune system: complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity. Additional purported mechanisms of action include induction of apoptosis through Fc receptor-mediated daratumumab crosslinking, antibody-dependent cellular phagocytosis, and activation of caspase-dependent multiple myeloma cell death.¹⁸⁹ Daratumumab is administered intravenously at a dosage of 16 mg/kg once weekly for the first 8 weeks of treatment, then every 2 weeks for weeks 9–24, then every 4 weeks from week 25 until disease progression.^{187,190}

Elotuzumab is a humanized, immunoglobulin G1 monoclonal antibody specific for SLAMF7 (signaling lymphocyte activation molecule family member 7). SLAMF7 (also known as CD2 subunit 1 [CS1] or CD319) is a transmembrane glycoprotein that researchers have observed to be expressed at high levels on myeloma cells.¹⁹¹ The primary mode of action is thought to be the induction of antibody-dependent cell-mediated cytotoxicity in which elotuzumab bound to SLAMF7 on the surface of myeloma cells activates natural killer (NK) cell cytotoxic activity; however, additional mechanisms of action have been hypothesized.¹⁹¹ Elotuzumab is intended to be used in combination with lenalidomide and dexamethasone. The drug is administered intravenously at a dosage of 10 mg/kg once weekly for the first of two 28-day cycles and once every 2 weeks thereafter.^{185,192}

Clinical trials: The phase II, single-group assignment Sirius trial studied daratumumab monotherapy in patients with multiple myeloma who had undergone at least three prior treatments (including a proteasome inhibitor and an immunomodulatory drug).¹⁹⁰ Investigators reported an overall response rate of 29.2% among patients receiving daratumumab at 16 mg/kg (n=106). Additionally, investigators reported a median progression-free survival of 3.7 months and a median duration of response of 7.4 months among responders. A similar response rate for daratumumab monotherapy of 35.7% (15/42) was reported in the phase II portion of the phase I/II GEN501 trial, which also enrolled patients with heavily pretreated multiple myeloma.^{193,194}

In the Sirius trial, the following adverse events were experienced by at least 20% of patients receiving the 16 mg/kg dose of daratumumab: fatigue (39.6%), anemia (33.0%), nausea (29.2%), thrombocytopenia (25.5%), back pain (22.6%), neutropenia (22.6%), and cough (20.8%). Five patients (4.7%) discontinued daratumumab treatment because of adverse events; however, none of these adverse events were attributable to daratumumab treatment, according to investigators.¹⁹⁰ Daratumumab's prescribing information also carries a warning about the potential for infusion

reactions, which occurred in more than 20% of patients receiving daratumumab infusions.¹⁸⁷ Phase III, manufacturer-sponsored trials of daratumumab in combination with both bortezomib- and lenalidomide-containing regimens in both relapsed/refractory and previously untreated disease are ongoing.¹⁹⁵⁻¹⁹⁸

Elotuzumab was studied in a randomized, open-label, phase III trial (ELOQUENT-2), in which 646 patients with relapsed or refractory multiple myeloma (1 to 3 prior lines of therapy) were randomly assigned to treatment with elotuzumab, lenalidomide, and low-dose dexamethasone or to treatment with lenalidomide plus low-dose dexamethasone.¹⁸⁵ After a median followup of 24.5 months, investigators reported progression-free survival of 19.4 and 14.9 months in the elotuzumab group and control group, respectively (HR 0.70; 95% CI, 0.57 to 0.85; $p < 0.001$). Additionally, investigators reported an overall response rate of 79% and 66% in the elotuzumab group and control group, respectively ($p < 0.001$).

Adding elotuzumab to lenalidomide was associated with only a modest increase in adverse events: 65% of patients in the elotuzumab group experienced a severe adverse event compared with 57% of patients in the control group. In particular, grade 3 or 4 lymphocytopenia was reported in 77% of patients in the elotuzumab group compared with 49% of patients in the control group. However, rates of other hematologic adverse events were similar between the two arms, as follows:¹⁹⁰

- Grade 3 or 4 anemia (19% elotuzumab vs. 21% control)
- Thrombocytopenia (19% vs. 20%)
- Neutropenia (34% vs. 44%)

An additional manufacturer-sponsored phase III trial (ELOQUENT-1) is studying the combination of elotuzumab, lenalidomide, and dexamethasone in patients with previously untreated multiple myeloma.^{199,200}

Manufacturer and regulatory status: Daratumumab is being developed by Janssen Research & Development, a unit of Johnson & Johnson, (New Brunswick, NJ), which licensed the compound from GenMab a/s (Copenhagen, Denmark).²⁰¹ In May 2013, FDA granted daratumumab breakthrough therapy status for treating patients who have multiple myeloma and have received at least three lines of therapy previously, including a proteasome inhibitor and an immunomodulatory agent.²⁰² In July 2015, Janssen completed a biologics license application to FDA based on data from the phase II Sirius trial and the phase I/II GEN501 trial.²⁰³ In November 2015, after a priority review, FDA granted daratumumab accelerated approval for treating “patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.”^{187,199,204}

Elotuzumab is being codeveloped by Bristol-Myers Squibb (New York, NY) and AbbVie (North Chicago, IL). The companies submitted a biologics license application for elotuzumab based on the data from the ELOQUENT-2 trial.²⁰⁵ In November 2015, after priority review, FDA approved elotuzumab for use in combination with two other therapies (lenalidomide and dexamethasone) for treating multiple myeloma in patients who have received one to three prior treatments.¹⁸⁸ FDA had granted breakthrough therapy status to elotuzumab for this indication.²⁰⁶

Diffusion and cost: Johnson & Johnson has reportedly priced daratumumab at \$5,850 per infusion for an 80 kg person. At the FDA-approved dosing, this would equate to an annual cost of \$135,550 in treatment year 1 and \$76,044 in subsequent years.²⁰⁷ Bristol-Myers Squibb and AbbVie have priced elotuzumab similarly, with the cost of the first year’s treatment estimated to be \$142,000.²⁰⁸ Adoption of daratumumab and elotuzumab will likely further increase the already high

cost of multiple myeloma treatment, particularly when used in combination with immunomodulatory drugs or proteasome inhibitors.

Clinical Pathway at Point of This Intervention

In the first-line treatment setting, the National Comprehensive Cancer Network (NCCN) guideline for treating multiple myeloma includes five preferred treatment regimens for patients ineligible for stem cell transplant:¹⁸⁴

- Bortezomib and dexamethasone
- Lenalidomide and dexamethasone
- Melphalan, prednisone, and bortezomib
- Melphalan, prednisone, and lenalidomide
- Melphalan, prednisone, and thalidomide

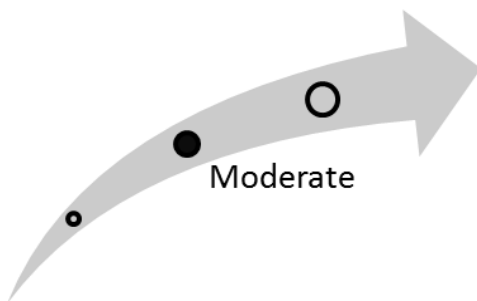
In the relapsed or refractory treatment setting, the NCCN guideline includes a number of preferred regimens as treatment options. For patients who experienced disease relapse at least 6 months after completing initial therapy, repeating the initial treatment regimen is an option. Alternative treatment regimens with a category 1 recommendation from NCCN include:¹⁸⁴

- Bortezomib monotherapy
- Bortezomib and liposomal doxorubicin
- Carfilzomib, lenalidomide, and dexamethasone
- Lenalidomide and dexamethasone
- Panobinostat, bortezomib, and dexamethasone

Although several treatment options are available for patients with recurrent or refractory disease, treatment options are more limited for patients who have undergone multiple rounds of treatment and whose regimens included both an immunomodulatory agent and a proteasome inhibitor.¹⁸⁹

Daratumumab and elotuzumab would be expected to compete with and/or complement these existing treatment regimens. Initial approval of daratumumab is for use as a monotherapy in heavily pretreated patients where it would be expected to compete with treatments such as carfilzomib or pomalidomide.¹⁸⁷ Initial approval of elotuzumab is for use in combination with lenalidomide and dexamethasone in patients who have undergone at least one round of therapy,¹⁹² a setting in which it would complement standard treatments such as lenalidomide and dexamethasone and compete with other treatment alternatives (e.g., carfilzomib, lenalidomide, and dexamethasone).

Figure 6. Overall high-impact potential: monoclonal antibodies (daratumumab [Darzalex], elotuzumab [Empliciti]) for treatment of multiple myeloma



Overall, experts commenting suggested that the improvements in progression-free survival observed for daratumumab and elotuzumab in patients with recurrent/refractory multiple myeloma represent an important advance in treating this incurable disease. For these reasons, the majority of

experts commenting envisioned that the drugs would be widely adopted for treating these patients. Additionally, experts suggested that these drugs could add substantially to the cost of treating patients who have multiple myeloma, potentially worsening any existing health disparities based on economic status or access to insurance coverage. Although these drugs are the first infused monoclonal antibody treatments for multiple myeloma, commenters did not believe that this would cause substantial disruption to health care facility staffing or infrastructure because health care workers are familiar with using infused therapies for cancer treatment.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on daratumumab for treating multiple myeloma,²⁰⁹⁻²¹⁴ and six experts, with similar backgrounds, offered perspectives on elotuzumab for treating multiple myeloma.²¹⁵⁻²²⁰ Four experts commented on both interventions.^{209,210,212,213,215,216,219,220} We have organized the following discussion of expert comments according to the parameters on which they commented.

Daratumumab

Unmet need and health outcomes: The unmet need for more effective multiple myeloma treatments was seen as moderately to very important by experts commenting, citing the need for novel treatments for this chronic, incurable disease. In particular, multiple commenters noted that new approaches are needed for patients with disease previously treated with both immunomodulatory drugs and proteasome inhibitors, the patient population studied in the phase II trial of daratumumab. One expert with a clinical perspective noted that the demonstrated single-agent activity of daratumumab in this double-refractory patient population is an important addition to available treatment options.²⁰⁹

Daratumumab's potential to improve patient health was also viewed favorably by the majority of experts commenting, citing the promising response rates and acceptable adverse event profile observed in the heavily pretreated patient population studied in the Sirius trial. However, multiple commenters observed that the evidence base was small, consisting of a single trial lacking a control group. One commenter with a research perspective suggested that daratumumab has only minimal potential to improve patient health because of the limited evidence base and because many of the responses reported in the Sirius trial were only partial responses.²¹⁴ Several commenters noted that further studies are needed to determine the drug's full impact, in particular data from ongoing randomized control trials of daratumumab in combination with standard treatment.

Acceptance and adoption: Most commenters thought daratumumab is likely to be adopted widely by both patients and physicians. Patients would prefer receiving treatment with an antibody instead of traditional chemotherapy, a clinician suggested.²⁰⁹ An expert with a research perspective noted that as an IV medication, daratumumab would be less convenient than alternative options but would be adopted in the light of clinical data demonstrating a significant improvement in patient outcomes.²¹¹ Another expert opined that patients with refractory multiple myeloma would be inclined to try daratumumab even if evidence of its efficacy is limited.²¹² In terms of physician acceptance, however, one expert with a research perspective thought limited clinical data would be a barrier to physicians adopting daratumumab.²¹²

Health care delivery infrastructure and patient management: Daratumumab has little potential to affect health care delivery infrastructure and patient management, most experts concurred. Infusion centers already have the staff and infrastructure necessary for administering intravenous cancer drugs. Similarly, patients receiving treatment for multiple myeloma have already been treated with intravenous interventions (e.g., carfilzomib, cyclophosphamide) when they begin

their regimen with daratumumab. However, a clinician thought that because of its first-in-class status, daratumumab would be widely used to treat every patient with multiple myeloma as part of standard chemotherapy regimens recommended by NCCN.²⁰⁹

Health disparities: Experts noted daratumumab will be an expensive drug and double- and triple-combination regimens will bring costs up considerably. Making their comments before the FDA approval of daratumumab, three experts stated that even if FDA were to approve daratumumab, uninsured or underinsured patients would have limited access to treatment.^{209,211,213} Among hematologic malignancies, multiple myeloma is not common, although it affects more African Americans than Caucasians, an expert with a research perspective noted.²¹² However, this expert also suggested that despite being a costly drug, daratumumab would be used in small patient populations and would not increase health disparities.²¹²

Elotuzumab

Unmet need and health outcomes: The unmet need for more effective multiple myeloma treatments was seen as very important by the majority of experts commenting, citing the poor prognosis for patients whose disease has progressed after initial therapy. However, one expert commenter speaking from a clinical perspective suggested that the unmet need potentially addressed by elotuzumab was of only moderate importance. This individual observed that the only phase III trial data for elotuzumab were from combination therapy with lenalidomide and that the lack of demonstrated single-agent activity and the unlikelihood that elotuzumab plus lenalidomide would be used in patients previously treated with lenalidomide limited elotuzumab's potential use.²¹⁵

Elotuzumab's potential to improve patient health was viewed favorably by the majority of experts commenting, citing the promising improvements in response rates and progression-free survival and relatively low rates of adverse events observed in the ELOQUENT-2 trial. However, commenters also identified several potential limitations. Multiple commenters noted that only trial data from a single phase III trial are available. Two commenters with a research perspective noted that longer followup or additional trials would be needed to determine whether the improvements in response rate and progression-free survival translate to improvement in overall survival.^{218,219} Additionally, two commenters with clinical perspectives suggested that results of trials assessing the utility of elotuzumab in conjunction with other multiple myeloma agents (e.g., bortezomib, carfilzomib, pomalidomide) are needed.^{215,220}

Acceptance and adoption: Elotuzumab is likely to be adopted widely by both patients and physicians, according to the majority of experts commenting. Factors driving acceptance mentioned by multiple commenters included the promising safety and efficacy results observed in the ELOQUENT-2 trial and few barriers to adoption for a drug administered by standard intravenous infusion. However, one commenter with a clinical perspective noted that the multiple myeloma treatment landscape is quite crowded and, for this reason, envisioned only moderate adoption by clinicians.²¹⁵ Additionally, one commenter with a research perspective opined that clinicians would accept elotuzumab moderately, envisioning adoption by clinicians only for patients who have exhausted other treatment options.²¹⁸ This commenter also envisioned only minimal acceptance by patients, suggesting that the need for outpatient visits for infusions would limit patient enthusiasm for this option.²¹⁸

Health care delivery infrastructure and patient management: Elotuzumab would have only modest effects on health care delivery infrastructure and patients management according to experts commenting. Although commenters noted that use of elotuzumab in combination with lenalidomide and dexamethasone would require additional outpatient appointments to receive elotuzumab

infusions, this was not seen as representing an undue burden on patient management or health care infrastructure, given the standard use of intravenously infused drugs for many oncology indications.

Health disparities: Elotuzumab has little to no potential to address health disparities, according to the experts commenting. However, several commenters with noted that the high cost of the treatment could widen any existing disparities based on socioeconomic status.

Ruxolitinib (Jakafi) for Treatment of Polycythemia Vera

Unmet need: Polycythemia vera is a rare myeloproliferative disorder that affects about 100,000 individuals in the United States.^{221,222} Patients with high-risk polycythemia vera are typically treated with a form of cytoreductive therapy that aims to prevent and manage thrombotic and bleeding complications, control symptoms, and minimize risk of progression to more aggressive diseases (e.g., post-polycythemia vera myelofibrosis, acute myeloid leukemia).²²³ First-line treatment of high-risk polycythemia vera is typically hydroxyurea; however, for patients whose disease is not adequately controlled by hydroxyurea or who cannot tolerate it, a substantial unmet need exists for safe and effective therapies.²²⁴

Intervention: Ruxolitinib is an orally administered small-molecule inhibitor of two protein kinases (Janus kinase 1 and 2 [JAK1 and JAK2]) that play central roles in regulating myeloid lineages.²²⁵ Overactivation of Janus kinase pathway signaling has been linked to pathogenesis of polycythemia vera, and about 90% of polycythemia vera cases harbor an activating mutation in the gene encoding JAK2 (i.e., *JAK2V617F*).²²³ JAK2 overactivity is also thought to play a key role in the pathophysiology of the related myeloproliferative neoplasm myelofibrosis, a condition in which ruxolitinib has demonstrated clinical utility.²²⁴ On the basis of these observations, investigators have studied the potential use of ruxolitinib in treating patients who have polycythemia vera.

Clinical trials: Investigators studied ruxolitinib for treating patients with polycythemia vera in two phase III randomized control trials: RESPONSE and RELIEF.^{226,227} RESPONSE was an open-label trial in which patients (n=222) with polycythemia vera whose disease was resistant to hydroxyurea or who could not tolerate it were randomly assigned to receive ruxolitinib or best available therapy. Ruxolitinib was administered twice daily at a starting dose of 10 mg, which was titrated as needed (25 mg maximum). Best available therapy consisted of a physician's choice among hydroxyurea, pegylated interferon alfa, pipobroman, anagrelide, lenalidomide, pomalidomide, or phlebotomy. The trial's primary endpoint was the proportion of patients who achieved both hematocrit control without phlebotomy and a reduction in spleen volume of at least 35%. Investigators reported that the primary endpoint in the ruxolitinib and best available therapy arms was met in 21% and 1% of patients, respectively ($p<0.0001$).²²⁶

RELIEF was a double-blind trial in which patients (n=104) with polycythemia vera who were still reporting disease symptoms while on a stable hydroxyurea dose were randomly assigned to receive either ruxolitinib (dosed as in the RESPONSE trial above) or continued hydroxyurea. In each arm, patients also received a placebo matching the treatment in the alternate arm. The trial's primary endpoint was the percentage of patients at week 16 who achieved a 50% or greater reduction in the Myeloproliferative Neoplasm Symptom Assessment Form cytokine total symptom score (TSS-C), which measures patient-reported severity of symptoms (i.e., itching, tiredness, muscle ache, night sweats, and sweats while awake). Investigators reported that a "trend towards symptom improvement" was observed in patients assigned to ruxolitinib treatment, but it was not statistically significant; the percentage of patients achieving at least a 50% reduction in TSS-C from baseline to week 16 was 43.4% in the ruxolitinib arm and 29.6% in the hydroxyurea arm ($p=0.139$).²²⁷

Both hematologic and nonhematologic adverse events have been reported in patients taking ruxolitinib. The most common hematologic adverse events were thrombocytopenia and anemia. The most common nonhematologic adverse events were bruising, dizziness, and headache.²²⁸

Manufacturer and regulatory status: Ruxolitinib is being developed by Incyte Corp. (Wilmington, DE), in collaboration with Novartis International AG (Basel, Switzerland), which licensed the drug from Incyte for development and commercialization outside the United States.²²⁹ FDA approved ruxolitinib in 2012 for treating intermediate- or high-risk myelofibrosis, a

myeloproliferative neoplasm related to polycythemia vera.²²⁸ In June 2014, Incyte submitted a supplemental NDA to FDA, seeking a label expansion to include polycythemia vera in patients who have had an inadequate response to hydroxyurea or cannot tolerate it (the patient population enrolled in the RESPONSE trial).²³⁰ In December 2014, FDA approved ruxolitinib for treating “polycythemia vera patients who have an inadequate response to or cannot tolerate hydroxyurea.”²³¹

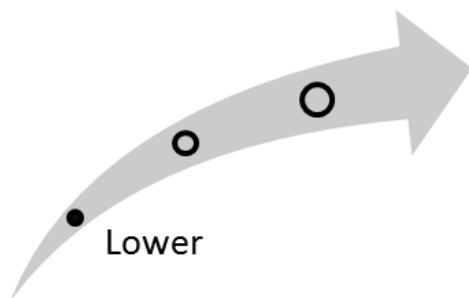
Diffusion and cost: As of November 2015, ruxolitinib (sixty 10 mg tablets as a 1-month supply) cost between \$9,955 and \$10,931 (average \$10,351).²³² Higher- and lower-dose tablets (5–25 mg) were priced similarly. This represents a 1-month supply of the drug; therefore, 1 year of ruxolitinib treatment would cost about \$125,000.

A search of 11 representative, private, third-party payers that publish their coverage policies online found several payers that included ruxolitinib in their formularies.^{233–237} Plans typically classify ruxolitinib as a specialty pharmaceutical and require prior authorization for coverage.

Clinical Pathway at Point of This Intervention

Physicians manage symptoms of the disease by using phlebotomy to maintain a hematocrit level of less than 45% and by using aspirin to reduce risk of thrombosis. For patients with intermediate- to high-risk polycythemia vera, cytoreductive therapy may also be used. Patients may be designated as higher risk if they do not tolerate phlebotomy well, require frequent phlebotomies to maintain target hematocrit, have high platelet counts, or exhibit progressive leukocytosis. First-line cytoreductive therapies include hydroxyurea and interferon-alfa. For patients who are intolerant of or fail to respond to first-line therapy, alternatives include pipobroman and busulfan; however, these treatments are typically reserved for patients with shorter life expectancies because of their potential to lead to leukemia.^{223,224}

Figure 7. Overall high-impact potential: ruxolitinib (Jakafi) for treating polycythemia vera



Overall, experts commenting on this intervention believe that ruxolitinib has potential to meet a significant unmet need, given the significant morbidity that patients with polycythemia vera experience and the lack of approved treatments. In terms of improving health, the majority of commenters suggested ruxolitinib has substantial potential to improve health for patients with polycythemia vera, citing the efficacy demonstrated in the RESPONSE trial, the relatively benign safety profile, and the lack of existing safe and effective treatments. However, experts also suggested that because of its routine mode of administration, ruxolitinib’s adoption for treating patients with polycythemia vera would have only minimal impacts on health care infrastructure and patient management. Based on these mixed perspectives, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this topic.²³⁸⁻²⁴³ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts commenting indicated that the need for novel treatments for polycythemia vera is moderately to very important, citing the limited treatment options for patients with the disease. In particular, one clinical expert noted that cytoreductive therapies used off label do not prevent progression to more aggressive diseases such as myelofibrosis or leukemia; therefore, treatments with the potential to improve these outcomes are highly sought.²⁴³ Additionally, a second commenter with a clinical perspective noted that a large need exists for treatments with the potential to induce polycythemia vera remissions.²³⁸

The majority of commenters also suggested that ruxolitinib has moderate potential to improve patient health, citing the improvement in polycythemia vera symptoms and acceptable adverse event profile reported in clinical trials of the drug. One expert with a clinical perspective who had first-hand experience prescribing the drug indicated that its potential to improve patient health was large, indicating that he considered the drug a safe and effective treatment option for controlling polycythemia vera symptoms and blood counts.²³⁸ Conversely, one commenter with a research perspective suggested that the limited data available on the treatment at this time left questions as to whether ruxolitinib was a significant improvement over available treatments and so has only minimal potential to improve patient health.²⁴¹

Acceptance and adoption: Moderate to wide adoption of ruxolitinib by clinicians and patients is likely, according to the majority of experts commenting. Factors promoting ruxolitinib adoption include convenience of oral administration, the lack of other polycythemia vera treatment options (particularly for patients whose disease does not respond to existing treatments), the manageable adverse-event profile, and the potential for patients to reduce their dependence on phlebotomy treatments. Factors that could limit ruxolitinib adoption include the high cost of the treatment and the unclear extent of ruxolitinib's benefit, given the preliminary nature of the data.²⁴¹

Health care delivery infrastructure and patient management: Ruxolitinib would cause little to no change in health care facility staffing or infrastructure, according to experts commenting. They cited the oral medication's ease of administration, and one expert speaking from a clinical perspective suggested that the types of adverse events arising from ruxolitinib treatment could easily be managed in the outpatient setting.²³⁸

Health disparities: Ruxolitinib has no potential to improve health disparities, according to experts commenting. Several commenters suggested that its high cost could exacerbate existing health disparities based on socioeconomic status.

Siltuximab (Sylvant) for Treatment of Multicentric Castleman's Disease

Unmet need: Castleman's disease (also known as giant lymph node hyperplasia or angiofollicular lymph node hyperplasia) is a rare lymphoproliferative disorder that manifests as enlarged lymph nodes caused by accumulating nonclonal B cells.²⁴⁴ Patients with multicentric Castleman's disease experience significant morbidity. Few treatment options are available, and disease recurrences are common.²⁴⁵ Novel treatments are needed.

Intervention: Overproduction of the pleiotropic cytokine interleukin-6 (IL-6) has been implicated in the pathogenesis of Castleman's disease.²⁴⁵ Evidence suggesting a role for IL-6 in Castleman's disease comes from multiple sources. Researchers have observed elevated levels of IL-6 in patients with the disease. Animal models in which IL-6 expression was experimentally elevated developed symptoms consistent with Castleman's disease. Lastly, a link between human herpes virus-8 (HHV-8) infection and Castleman's disease has been attributed to the production of a viral IL-6 ortholog, vIL-6 (an orthologous gene is one present in different species that evolved from a common ancestor).²⁴⁶ Thus, researchers have hypothesized that blocking IL-6 activity could ameliorate the symptoms of Castleman's disease.^{246,247}

Siltuximab is a chimeric monoclonal antibody for IL-6. Antibody binding to IL-6 may neutralize the cytokine, preventing it from exerting its pathogenic effects.²⁴⁷ In clinical trials for treating Castleman's disease, siltuximab is being administered in a 1-hour infusion at a dose of 11 mg/kg. Infusions are given once every 3 weeks, and the treatment may go on indefinitely, barring disease progression or unacceptable toxicity in the patient.^{248,249}

Clinical trials: Siltuximab was studied in a 79-patient, placebo-controlled, double-blind randomized trial in which patients were assigned in a 2:1 ratio to treatment with either siltuximab or placebo.²⁵⁰ Although Castleman's disease is frequently associated with HHV-8 infection in HIV-positive patients, HHV-8 and HIV-positive patients were excluded from the trial because siltuximab did not demonstrate binding to viral IL-6 in a preclinical trial.²⁵¹ The primary endpoint of the trial was the number of patients who achieved a tumor response and a reduction in symptoms. In the trial, a higher percentage of patients in the siltuximab arm achieved a durable tumor and symptom response than did patients in the placebo arm (34% vs. 0%; $p=0.0012$). The rate of treatment-emergent adverse events was similar in the siltuximab and placebo groups, despite patients receiving siltuximab for more than twice as long as patients receiving placebo (median 375 vs. 152 days).²⁵⁰ Grade 3 or above adverse events were reported in 47% of patients receiving siltuximab versus 54% of patients receiving placebo, and severe adverse events were reported in 23% of patients receiving siltuximab versus 19% of patients receiving placebo.²⁴⁸ The most common adverse events that occurred at least 10% more often in patients receiving siltuximab than placebo were hyperuricemia, increased weight, pruritus, rash, and upper respiratory tract infection.²⁵¹

Manufacturer and regulatory status: Siltuximab was developed by the Janssen Biotech unit of Johnson & Johnson (New Brunswick, NJ). In April 2014, FDA approved siltuximab for treating patients with multicentric Castleman's disease "who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative."^{251,252} The siltuximab biologics license application was reviewed under FDA's priority review program.^{252,253}

Diffusion and cost: As of November 2015, retail prices for 100 mg and 400 mg vials of siltuximab for infusion were reportedly about \$910 and \$3,750, respectively.^{254,255} A 70 kg (154 lb) adult at a dose of 11 mg/kg administered once every 3 weeks would require about two 400 mg vials per treatment, which would cost about \$7,500 per treatment, or \$130,000 per year. The drug is intended to be taken on an ongoing basis as long as the patient benefits from therapy.²⁵¹

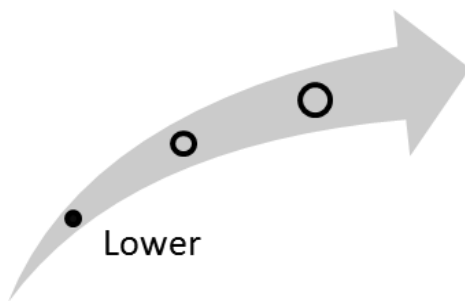
Our searches of 11 representative, private, third-party payers that publish their coverage policies online identified 5 policies regarding siltuximab, which indicated that the drug is considered medically necessary and covered for its FDA-approved indication.²⁵⁶⁻²⁶⁰ Two of these policies require prior authorization for coverage.^{257,258}

Clinical Pathway at Point of This Intervention

Siltuximab was the first drug approved by FDA for treating multicentric Castleman's disease; however, many systemic therapies have been used off label. These have included traditional cytotoxic chemotherapy as well as more recent additions, such as the anti-CD20 monoclonal antibody rituximab and the immunomodulatory drug thalidomide.^{244,245}

Several antibodies targeting IL-6 signaling exist besides siltuximab. Although the majority of these compounds are investigational and not commercially available, one anti-IL-6–receptor antibody, tocilizumab, is FDA approved for another condition, rheumatoid arthritis. Preliminary studies of tocilizumab for treating Castleman's disease have been conducted, and the drug could be prescribed off label for this indication.²⁴⁶

Figure 8. Overall high-impact potential: siltuximab (Sylvant) for treatment of multicentric Castleman's disease



Overall, experts commenting on this intervention concurred that siltuximab has potential to fill a significant unmet need, given results from a clinical trial and the fact that FDA has approved no other therapies for this indication. However, siltuximab's overall impact is limited by the small size of the affected patient population, the lack of any substantial changes to patient management or health care facility infrastructure, and the preliminary nature of the data on a therapy that could potentially be taken for extended periods. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this topic.²⁶¹⁻²⁶⁶ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need for novel therapies to treat Castleman's disease is moderately to very important according to experts commenting, who cited the lack of FDA-approved therapies for the condition and its significant morbidity. Although one health systems commenter suggested that the availability of several off-label treatments for treating patients with multicentric Castleman's disease limits the magnitude of the unmet need,²⁶¹ other commenters with clinical perspectives noted that no reliable treatment exists for this patient population, and the available treatments are often associated with substantial toxicity, which limits their long-term use for an individual.^{264,265} Although most commenters noted the lack of effective

therapies, the majority also noted that the small number of patients affected by this condition limits the magnitude of unmet medical need.

Siltuximab has minimal to moderate potential to improve patient health, according to experts' comments. Although commenters suggested that the phase II trial results that led to FDA approval were promising in terms of response rate, several commenters noted that this came at the expense of prolonged and sometimes severe adverse events. Experts were divided in their opinions regarding the risk-benefit profile of the treatment, with two suggesting the drug has only minimal potential to improve patient health^{261,265} and two suggesting that its potential was moderate.^{262,264} One expert with a research perspective noted that treatment may involve long-term therapy and longer-term studies of the treatment's impact on patient outcomes and quality of life are needed.²⁶⁶

Acceptance and adoption: Siltuximab is likely to be adopted by clinicians and patients, thought the majority of experts. These experts noted the lack of viable alternatives (in particular FDA-approved alternatives) and siltuximab's familiar mode of IV infusion as factors promoting clinician adoption. Additionally, one clinical expert noted that patients would be attracted to a treatment that has the potential for durable symptom control.²⁶⁴ However, a second clinical expert suggested that some patients could be dissuaded from the treatment because it requires ongoing infusions administered once every 3 weeks.²⁶⁵ One commenter with a health systems perspective suggested that siltuximab adoption would be minimal because of the potential for adverse events and the availability of off-label alternatives.²⁶¹

Health care delivery infrastructure and patient management: Siltuximab use would cause little to no change in health care facility staffing or infrastructure, the experts thought. They cited the familiar mode of IV infusion and the fact that patients with the disease are likely to have already received off-label IV treatment. Furthermore, experts thought that the small number of patients with multicentric Castleman's disease would limit any potential impacts in health care delivery and infrastructure.

Health disparities: The relatively high cost of siltuximab, combined with the need to receive infusions for an extended period of time, led commenters to conclude that adopting siltuximab would increase the cost of care for this patient population. This new therapy may exacerbate health disparities in uninsured or underinsured individuals because it may be unaffordable to patients with limited economic means.

Kidney Cancer Intervention

Checkpoint Inhibitor (Nivolumab [Opdivo]) for Treatment of Advanced Renal Cell Carcinoma

Unmet need: About 30% of renal cell carcinoma (RCC) cases are metastatic at the time of diagnosis.²⁶⁷ Although multiple RCC therapies targeting either VEGF or mTOR signaling have been approved in recent years, prognosis for these patients remains poor. In particular, for patients whose disease has progressed after first-line therapy, median overall survival is less than 2 years with available treatments.²⁶⁸

A different approach under study is inhibiting aberrantly activated immune checkpoints that suppress anticancer immune responses, an approach that may improve patient outcomes. Nivolumab (Opdivo®) is a monoclonal antibody that targets the programmed death-1 (PD-1) receptor, a component of one such immune checkpoint pathway. Late-phase clinical trials are testing nivolumab as monotherapy in previously treated metastatic RCC and in combination with ipilimumab for treating newly diagnosed, metastatic RCC.^{267,269,270}

Intervention: Evading destruction by the body's immune system is a hallmark of cancer, and researchers have identified multiple mechanisms by which cancers induce immune tolerance.^{271,272} One such mechanism is the co-option by tumors of endogenous mechanisms that limit T-cell responses. These so-called immune checkpoints are thought to have evolved to prevent runaway immune responses; however, by aberrantly activating these immune checkpoints, cancers purportedly can reduce the body's anticancer immune response.²⁷²

PD-1 is a central player in one of these checkpoint pathways.²⁷² It is expressed by many immune-system cells, including high expression on activated T cells. Research has demonstrated that in many cases, the tumor microenvironment expresses a ligand for PD-1 (PD-L1). Binding of PD-L1 to PD-1 is thought to induce T-cell anergy (diminished response to persistent antigen exposure). This anergy in the effector phase of the immune response limits tumor rejection.²⁷³ Disrupting the immune tolerance—inducing signaling between tumor-expressed PD-L1 and immune cell-expressed PD-1 is a therapeutic target that could potentially induce an immune response to the cancer by “releasing a brake” placed on the immune response through the PD-1 signaling pathway.²⁷²

Nivolumab is a fully humanized, immunoglobulin G4 monoclonal antibody highly specific for PD-1. Preclinical studies performed in cancer animal models have shown that antibody-mediated inhibition of the PD-1/PD-L1 pathway increases T-cell antitumor response.^{274,275} Nivolumab binding to PD-1 purportedly prevents the interaction between PD-1 and its ligands, preventing activation of the immune checkpoint and leading to an increase in anticancer immune response.^{274,276-281}

Clinical trials: The phase III clinical trials CheckMate 214 and CheckMate 025 are testing the safety and efficacy of nivolumab in the first- and second-line settings, respectively.^{269,270} In the CheckMate 214 trial, treatment-naïve patients are being treated with nivolumab (3 mg/kg, IV, every 2 weeks) after 4 cycles of ipilimumab (1 mg/kg, intravenous, every 3 weeks) and this regimen is being compared with the standard treatment sunitinib (50 mg daily, orally, for 4 weeks on and 2 weeks off). In September 2015, results from the CheckMate 025 trial were published in which safety and efficacy of nivolumab (3 mg/kg, intravenously, every 2 weeks) were compared with everolimus (10 mg, daily, orally) in 821 patients with progressive RCC after 1 or 2 angiogenic inhibitor therapies. The trial met its primary endpoint of improving overall survival; the median overall survival was 25 months with nivolumab and 19.6 months with everolimus (95% CI, 21.8 to not estimable vs. 95% CI, 17.6 to 23.1); and the hazard ratio with nivolumab against everolimus was 0.73 (98.5% CI, 0.57 to 0.93; p=0.002). Nivolumab also demonstrated better response rates

(25% vs. 5%; odds ratio, 5.98; 95% CI, 3.68 to 9.72; $p < 0.001$) and progression-free survival (4.6 vs. 4.4 months; HR, 0.88; 95% CI, 0.75 to 1.03; $p < 0.11$) than everolimus.²⁶⁷ Overall, nivolumab was well tolerated and caused fewer drug-related adverse events than everolimus. Potential safety concerns for patients ($n=821$) included the following grade 3 and 4 drug-related toxicities reported in the phase III CheckMate 025 trial, as compared with everolimus:²⁶⁷

- Anemia (2% with nivolumab vs. 8% with everolimus)
- Fatigue (2% vs. 3%)
- Diarrhea (1% vs. 1%)
- Dyspnea (1% vs. 1%)
- Hyperglycemia (1% vs. 4%)
- Pneumonitis (1% vs. 3%)
- Hypertriglyceridemia (0% vs. 5%)
- Mucosal inflammation (0% vs. 3%)
- Stomatitis (0% vs. 4%)

Manufacturer and regulatory status: Nivolumab is being developed by Bristol-Myers Squibb (New York, NY) for treating various types of cancer. In July 2015, the phase III CheckMate 025 trial was stopped early after an independent data monitoring committee concluded the study had met its endpoint and patients treated with nivolumab showed improved survival, compared with everolimus treatment.²⁸² Results from CheckMate 025 were the basis for FDA to grant breakthrough therapy status in September 2015.²⁸³ FDA approved nivolumab in November 2015, under its priority review program, for treating advanced RCC after antiangiogenic therapy.^{284,285}

The drug has also been approved for use in other cancers. FDA approved nivolumab in December 2014 for treating advanced melanoma not responsive to ipilimumab or a BRAF inhibitor if the disease has the *BRAF*^{V600} mutation^{286,287} and in March 2015 for treating metastatic nonsmall cell lung cancer (NSCLC) in patients whose disease has progressed after treatment with platinum-based chemotherapy.^{288,289} In 2013, FDA had granted fast-track status for treating NSCLC, melanoma, and RCC.²⁹⁰

Diffusion and cost: As of October 2015, nivolumab cost was about \$2,500 for a 100 mg vial.²⁹¹ Nivolumab is administered intravenously at a dosage of 3 mg/kg every 2 weeks for treating melanoma and NSCLC, which is the same dose used for treating patients with RCC in CheckMate 025.^{267,292} Therefore, a patient weighing an average of 70 kg would require 210 mg (about 2 vials) costing \$5,250 per infusion, which would total about \$136,500 per year.

The Bristol-Myers Squibb Patient Assistance Foundation, Inc., was established to help uninsured patients who have a yearly income that is less than 250% of the Federal poverty level to help pay temporarily for medications, including nivolumab.²⁹³

CMS has not issued a national coverage determination for nivolumab. Drugs intended to treat patients who have cancer are typically covered for their FDA-approved indications. A search of 11 representative, private, third-party payers that publish their policies online found 4 policies that cover nivolumab for treating melanoma and NSCLC.²⁹⁴⁻²⁹⁷ Due to the recency of its approval, use of nivolumab in treating RCC will likely be covered by third-party payers and clarified as they update their policies.

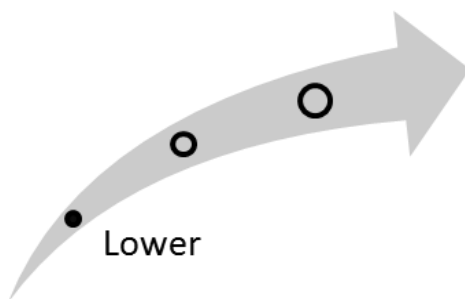
Clinical Pathway at Point of This Intervention

Cytotoxic chemotherapy has not demonstrated substantial activity in treating RCC, unlike many other cancers, and clinicians rely on targeted therapies to treat patients who have advanced disease.²⁶⁸ Treatments for metastatic clear cell RCC involve drugs that target the VEGF pathway (e.g., axitinib, pazopanib, sorafenib, sunitinib) or the mTOR pathway (e.g., everolimus,

temsirolimus).^{268,298} Although formal studies addressing the sequencing of these agents have not been completed, a VEGF pathway–targeting agent (frequently sunitinib or pazopanib) is typically used as a first-line treatment. Patients who experience disease progression may be switched to a second VEGF pathway–targeting agent or may be switched to an mTOR pathway agent.²⁶⁷

Nivolumab is under study in two late-phase RCC trials: (1) as a monotherapy in treating patients with RCC whose disease has progressed after one or more antiangiogenic therapies, and (2) in combination with ipilimumab in treating patients with newly diagnosed RCC.^{269,270} In these settings, it is expected that nivolumab or nivolumab plus ipilimumab would compete with currently used targeted therapies.

Figure 9. Overall high-impact potential: nivolumab (Opdivo) for treatment of advanced renal cell carcinoma



Although nivolumab showed greater efficacy than everolimus in a clinical trial, two experts with clinical backgrounds thought nivolumab had a small potential to fulfill the unmet need. They thought that even with durable responses, improvement in progression-free survival was minimal.^{299,300} In contrast, the other experts considered the efficacy of nivolumab in outperforming everolimus to be promising for patients who have limited options when their disease does not respond to standard treatments.³⁰¹⁻³⁰⁴ Additionally, an expert commented that patients will appreciate a 6-month extension in their lives, which is rarely observed with most new cancer drugs.³⁰⁴ Because of limited options after patients no longer respond to treatment, experts anticipate clinicians and patients will accept nivolumab for treating RCC. Because it is an intravenous drug instead of an oral one, nivolumab will cause a small change in patient management, but will not disrupt health care infrastructure. Based on these mixed views of experts commenting, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on nivolumab for treating RCC.²⁹⁹⁻³⁰⁴ We have organized the following discussion of expert comments according to the parameters on which they commented. Please note that experts made their comments before FDA approved nivolumab for treating RCC in November 2015.

Unmet need and health outcomes: A need exists for novel interventions for patients with metastatic RCC because, as three experts pointed out, available therapies have limited effectiveness for treating the disease, resulting in shortened life expectancies.^{299,302,303} Another shortcoming of the standard of care may be that most RCCs are diagnosed after they have metastasized.³⁰³ An expert with a clinical perspective noted the potential nivolumab has in the second-line setting for treating refractory RCC and also mentioned the possibility of it being used in the first-line setting if it shows greater efficacy than VEGF inhibitors.³⁰⁰ An expert noted that nivolumab has potential to improve on standard treatments since it extended patient survival by 5–6 months;³⁰³ even if it does not seem

like much, patients and their families will appreciate any extension in life. Thus, nivolumab has a moderate potential to improve patient health, most experts concluded.

Acceptance and adoption: Both physicians and patients are likely to adopt nivolumab for treating RCC, because of trials showing improvement in survival, all experts concurred. Physicians who prescribe nivolumab will not require additional training to administer the drug. However, three experts anticipate health care staff will require additional training to monitor and manage possible autoimmune adverse events.^{299,301,302} An expert with a research perspective argued nivolumab has significantly improved outcomes in patients with other types of cancer and the medical community is eager to adopt it as monotherapy or in combination with ipilimumab for treating RCC.³⁰² Although a clinician expects no barriers for adopting nivolumab as a single agent, the added adverse events may hinder its adoption as part of a combination regimen.³⁰⁰

Health care delivery infrastructure and patient management: Many cancer drugs are administered intravenously to patients, and all of the experts agreed that nivolumab use will not cause disruption to the delivery infrastructure. However, standard of care for patients with RCC includes mostly oral drugs. Therefore, a slight shift in patient management will be necessary for patients to attend an infusion center to receive intravenous nivolumab, noted three experts.^{299,300,304} Additionally, an expert with a health systems perspective anticipates that use of nivolumab could delay the need for palliative or hospice care, affecting health care infrastructure and patient management.³⁰³

Health disparities: Nivolumab is an expensive drug with an annual cost of about \$137,000 that is not approved by FDA; thus, it has potential to increase disparities in patients with low socioeconomic status, an expert opined.³⁰² On the other hand, a clinical reviewer thought (before the FDA approval) that if nivolumab were to be approved and covered by insurance, there would be less potential to affect health disparities. However, minorities usually lack insurance or have plans with limited coverage and may not have equal access to nivolumab, opined a clinician.³⁰⁰ In contrast, two experts pointed out that the manufacturer's assistance program could help uninsured and underinsured patients access to nivolumab.^{299,303}

Lung Cancer Interventions

Checkpoint Inhibitors (Nivolumab [Opdivo], Pembrolizumab [Keytruda]) for Treatment of Nonsmall Cell Lung Cancer

Unmet need: Despite recent advances in targeted therapeutic agents that can be used in combination with platinum-based chemotherapy, prognosis and outcomes in patients with lung cancer are poor, and lung cancer remains the leading cause of cancer-related deaths in the world.³⁰⁵ In the United States, patients who have advanced NSCLC have a 5-year survival rate of 2% to 13%. Clearly, novel approaches are needed.³⁰⁶

Researchers have observed the potential of the immune system to be a tool to treat cancer.³⁰⁷⁻³⁰⁹ One approach under study is inhibiting so-called immune checkpoints, which reportedly suppress anticancer immune responses. Nivolumab (Opdivo®) and pembrolizumab (Keytruda®) are monoclonal antibodies that target the PD-1 receptor, a component of one such immune checkpoint pathway. Clinical trials are testing nivolumab and pembrolizumab for treating NSCLC in multiple treatment settings.^{277,279-281,310-313}

Intervention: Researchers have identified several strategies cancer cells have developed to avoid detection and destruction by the body's immune system.^{271,272} One such immune-tolerance mechanism involves tumor cells overexpressing ligands that limit T-cell responses. These so-called immune checkpoints are thought to have evolved to prevent runaway immune responses; however, by aberrantly activating these immune checkpoints, cancers reportedly can reduce the body's anti-cancer immune response.²⁷²

One of these checkpoint pathways is PD-1, a cell receptor expressed by many immune-system cells, including high expression on activated T cells, which has a central role in T-cell downregulation.²⁷² Research has demonstrated that in many cases, the ligand for PD-1 (PD-L1) is highly expressed by the tumor microenvironment. Binding of PD-L1 to PD-1 is thought to induce T-cell anergy (diminished response to persistent antigen exposure), limiting tumor rejection by tumor-specific T cells in the effector phase of the immune response.²⁷³ Disrupting the immune tolerance—inducing signaling between tumor-expressed PD-L1 and immune cell—expressed PD-1 is a therapeutic target that could potentially induce an immune response to the cancer by “releasing a brake” placed on the immune response through the PD-1 signaling pathway.²⁷²

Nivolumab is a fully humanized, immunoglobulin G4 monoclonal antibody highly specific for PD-1.²⁷⁵ Similarly, pembrolizumab is a humanized monoclonal antibody in which the Fc region has been modified to reduce the induction of antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity, which have the potential to deplete immune cells expressing PD-1.³¹⁴ Preclinical studies performed in animal cancer models have shown that antibody-mediated inhibition of the PD-1/PD-L1 pathway increases T-cell antitumor response.²⁷⁴ Nivolumab and pembrolizumab binding to PD-1 purportedly prevents the interaction between PD-1 and its ligands, preventing activation of the immune checkpoint and leading to an increase in anticancer immune response.^{274,276-281}

Nivolumab and pembrolizumab are administered by IV infusion. In phase I trials, researchers tested escalating doses of nivolumab for various cancers, from 0.3 to 10 mg/kg.^{274,315} In ongoing phase III trials, patients with NSCLC are given 3 mg/kg of nivolumab once every 2 weeks.³¹⁶⁻³¹⁹ Pembrolizumab, which FDA recently approved, has prescribing information recommending 2 mg/kg once every 3 weeks, and treatment may continue for up to 2 years.^{320,321}

Clinical trials: *Nivolumab.* The CheckMate trial program is testing nivolumab in the second-line setting for treating advanced/metastatic squamous NSCLC (CheckMate 017 and 153) or nonsquamous NSCLC (CheckMate 057) in patients whose disease has failed to respond to systemic platinum-based doublet chemotherapy. Nivolumab is also being studied as first-line treatment for

therapy-naïve patients with advanced/metastatic NSCLC who are positive for PD-L1 expression (CheckMate 026).

The phase III CheckMate 017 and CheckMate 057 trials are randomized, open-label trials of 272 patients with squamous NSCLC and 574 patients with nonsquamous NSCLC, respectively. Patients received intravenously administered nivolumab (3 mg/kg, once every 2 weeks) or intravenously administered docetaxel (75 mg/m², once every 3 weeks), and results from both trials were presented at the 2015 American Society of Clinical Oncology (ASCO) annual meeting.^{322,323} In the CheckMate 017 trial, superior overall survival was observed in patients receiving nivolumab compared with those receiving docetaxel (9.2 vs. 6.0 months; HR, 0.59; p=0.00025). Similarly, nivolumab also improved progression-free survival over docetaxel (3.5 vs. 2.8 months; HR, 0.62; p=0.0004) and response rate (20% vs. 9%; p=0.0083).³²⁴ In January 2015, an independent data monitoring committee concluded that the CheckMate 017 trial had met its endpoint, stopped the trial early, and recommended treating all patients in both groups with nivolumab.^{288,325}

Data from the CheckMate 057 trial also demonstrated a significant improvement in overall survival and response rate compared with docetaxel (overall survival, 12.2 vs. 9.4 months; HR, 0.73; p=0.00155; response rate, 19.2% vs. 12.4%; p=0.0235). In contrast, nivolumab did not demonstrate clinical benefit in progression-free survival over docetaxel (2.3 vs. 4.2 months; HR, 0.92; p=0.393), which may be associated with PD-L1 expression.³²⁶

Potential safety concerns for patients may include the following drug-related toxicities reported in the phase I MDX-1106-03 trial, in which patients were treated with 1, 3, or 10 mg/kg of nivolumab:²⁷⁴

- Infusion-related reaction (10%)
- Diarrhea (9%)
- Pruritus (6%)
- Hypothyroidism (3%)
- Pruritic rash (2%)
- Vitiligo (2%)
- Adrenal insufficiency (1%)
- Erythema (1%)
- Erythematous rash (1%)
- Macular rash (1%)

Pembrolizumab. Through the KEYNOTE clinical program, pembrolizumab is being studied as an adjuvant (KEYNOTE-091), first-line (KEYNOTE-024 and KEYNOTE-042), and second-line therapies (KEYNOTE-001 and KEYNOTE-010) for treating NSCLC expressing high levels of PD-L1.^{310-313,327} In May 2015, Garon and collaborators published results from the phase I KEYNOTE-001 trial, in which 3 doses of pembrolizumab (2 mg/kg once every 3 weeks, 10 mg/kg once every 2 weeks, or 10 mg/kg once every 3 weeks) were assessed in 495 patients with advanced NSCLC. Pembrolizumab was proved to be beneficial among all patients; they achieved median objective response rates of 19.4% with a median duration of response of 12.5 months, median progression-free survival of 3.7 months, and median overall survival of 12 months. Based on the percentage of cells expressing PD-L1, patients were divided in the validation (>50% PD-L1) and training (<50% PD-L1) groups. Among patients in the validation group, the response rate was 45.2%, median progression-free survival was 6.3 months, and median overall survival was not reached at the time of the analysis.³²⁸

Patients enrolled in the phase I KEYNOTE-001 trial manifested the following grade 3 and higher pembrolizumab-related toxicities, which showed no clear difference among different dose regimens:³²⁸

- Dyspnea (3.8%)
- Pneumonitis (1.8%)
- Asthenia (1%)
- Decreased appetite (1%)

Adverse events. Similar to other immunotherapies, nivolumab also has the potential to lead to autoimmune or other immune-system disorders, which were observed in 81 of 207 patients (39%) and included rash, autoimmune thyroiditis, hepatitis, and one case each of sarcoidosis, endophthalmitis, diabetes mellitus, and myasthenia gravis.²⁷⁴ Pembrolizumab's prescribing information carries warnings about the potential for the following immune-related adverse events: colitis, endocrinopathies (i.e., hypophysitis [inflammation of the pituitary gland], thyroid disorders, type 1 diabetes mellitus), hepatitis, nephritis, and pneumonitis.³²⁹

Manufacturer and regulatory status: Nivolumab is being developed by Bristol-Myers Squibb (New York, NY) for treating various types of cancer. After granting priority review in February 2015, FDA approved nivolumab in March 2015 under its accelerated approval program, for treating metastatic, squamous NSCLC in patients whose disease has progressed after treatment with platinum-based chemotherapy.^{288,289} The approval was based on overall survival benefit observed in the phase III CheckMate 017 trial and the safety profile observed in the phase II CheckMate 063 trial.²⁸⁸ On the basis of safety and efficacy results from the phase III CheckMate 057 trial, FDA expanded the use of nivolumab, approving it for treating patients with nonsquamous NSCLC, in October 2015.³³⁰

Pembrolizumab is being developed by Merck & Co., Inc. (Whitehouse Station, NJ). In October 2014, FDA granted pembrolizumab breakthrough therapy status for treating advanced NSCLC.³³¹ In April 2015, citing results from the phase I KEYNOTE-001 trial, the company submitted a supplemental biologics license application (sBLA) to FDA. In June 2015, FDA granted priority review to the sBLA for treating squamous or nonsquamous NSCLC expressing high levels of PD-L1 that has progressed after treatment with platinum-based chemotherapy doublet and, if activating variants in the *EGFR* or *ALK* genes are present, treatment with EGFR and ALK inhibitors.^{332,333} In October 2015, FDA granted accelerated approval to pembrolizumab for this indication.³³⁴ At that time, FDA also announced the approval of a companion diagnostic test for pembrolizumab intended to assess PD-L1 expression in tumor samples (the PDL-1 IHC 22C3 pharmDx test, Dako North America, Inc., Carpinteria, CA).³³⁴

Diffusion and cost: Nivolumab reportedly costs about \$2,500 for a 100 mg vial.³³⁵ The prescription information states nivolumab is administered at a dosage of 3 mg/kg every 2 weeks for treating NSCLC.³³⁶ Therefore, a patient weighing an average of 70 kg would require 210 mg (about 2 vials), costing \$5,250 per infusion, which would total about \$136,500 per year.

Pembrolizumab reportedly costs about \$6,600 for 3 vials of 50 mg, which is roughly the amount (about 150 mg) a patient would use for a single 3-week treatment cycle for NSCLC.³³⁷ If a patient continued on treatment for a full year, the cost would be about \$112,200 (17 cycles at \$6,600 per cycle). The manufacturer offers a program to provide financial assistance to select patients who do not have health insurance, who have health plans that do not cover the drug, or who have coverage but cannot afford copayments.³³⁸

CMS has not issued an NCD for nivolumab or pembrolizumab. Drugs intended to treat cancer are typically covered for their FDA-approved indications. Our searches of 11 representative, private, third-party payers that publish their policies online found 4 policies that cover nivolumab for treating NSCLC that has progressed after platinum-based doublet chemotherapy, but found none for pembrolizumab; policies probably have not been updated for the recent NSCLC indication.³³⁹⁻³⁴²

Use of nivolumab and pembrolizumab in treating metastatic NSCLC will likely be covered by many third-party payers.

Clinical Pathway at Point of This Intervention

Treatment for NSCLC depends on the patient's condition, the cancer stage, tumor histology, and whether genetic alterations that may have triggered the oncogenic process have been identified in the patient's cancer. For advanced/metastatic NSCLC, systemic treatments are used.

Typical first-line treatment for metastatic/unresectable disease is platinum-doublet therapy, in which carboplatin or cisplatin is combined with a second agent (e.g., docetaxel, etoposide, gemcitabine, irinotecan, paclitaxel, pemetrexed, vinblastine, vinorelbine).³⁴³ In the event that NSCLC continues to grow or spread after these first-line treatments, patients may be switched to a different cytotoxic chemotherapy (e.g., docetaxel, gemcitabine, pemetrexed).³⁴³ However, in the case of cancers bearing an activating mutation in the *EGFR* or the *ALK* gene, EGFR inhibitors (e.g., afatinib, erlotinib, gefitinib) or ALK inhibitors (e.g., crizotinib) are the standard of care in the first-line setting.³⁴³⁻³⁴⁵ These genetic drivers occur more frequently in nonsquamous cancers, and cancers with squamous histology may not routinely undergo genetic analysis.

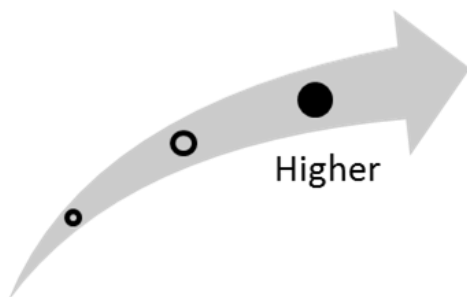
Initially, nivolumab and pembrolizumab would be administered in patients whose disease has progressed after platinum-based chemotherapy and any targeted therapies for which the patient is eligible.³³⁴ In this setting, checkpoint inhibitors are expected to compete with available salvage chemotherapy regimens.

Nivolumab (CheckMate 026 trial) and pembrolizumab (KEYNOTE-024 and KEYNOTE-042 studies) are also under study in the first-line setting for treating unresectable/metastatic lung cancer. In the first-line setting, checkpoint inhibitors are expected to compete with conventional platinum-based chemotherapy regimens.^{280,311,312} They could also compete with targeted therapies (e.g., ALK inhibitors, EGFR inhibitors) in this setting; however, patients with actionable driver mutations are being excluded from ongoing trials testing checkpoint inhibitors in the first-line setting.

Lastly, pembrolizumab is being studied in patients with early stage disease after completing surgical resection and any adjuvant chemotherapy (KEYNOTE-091 study), a setting in which no standard therapy is used.³¹³

Immune checkpoint inhibitors are a highly active area of investigation, and multiple monoclonal antibodies targeting PD-L1 in tumor cells (e.g., avelumab [MSB0010718C], atezolizumab [MPDL3280A], durvalumab [MEDI4736]) are under study that could compete with nivolumab and pembrolizumab, if approved.³⁴⁶⁻³⁴⁸

Figure 10. Overall high-impact potential: checkpoint inhibitors (nivolumab [Opdivo], pembrolizumab [Keytruda]) for treatment of nonsmall cell lung cancer



Overall, most experts commenting on these interventions thought nivolumab and pembrolizumab have significant potential to improve outcomes in patients with NSCLC, who currently have limited treatment options. Further, if results from additional studies continue to be

favorable and the role of PD-L1 in cancer is better understood, checkpoint inhibitors may offer more benefit than standard treatments. The experts anticipate that if the available clinical data suggest they can be a novel option for treatment-resistant NSCLC, nivolumab and pembrolizumab will be widely adopted by physicians and patients. Because they are administered intravenously, checkpoint inhibitors will affect neither health care infrastructure nor patient management. In a contrasting opinion, some experts thought that the onset of serious adverse events caused by immunotherapy could be a hurdle for adoption. Experts also agree checkpoint inhibitors are very expensive and have a high potential to increase health care costs; whether costs will be absorbed mostly by third-party payers or patients remains to be determined because it will depend on coverage and any discounts negotiated by payers with the company. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on nivolumab,³⁴⁹⁻³⁵⁴ and six experts, with similar backgrounds, offered perspectives on pembrolizumab for treating advanced NSCLC.³⁵⁵⁻³⁶⁰ Of these, two commented on both nivolumab and pembrolizumab.^{351,353,355,358} We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Five-year survival for patients with NSCLC ranges from 2% to 13%, and most die within the first year of diagnosis, so all experts agreed a great need exists for targeted options that improve survival. One expert thought nivolumab would be favorable in tumors overexpressing PD-L1, in particular, because some evidence shows nivolumab improves survival in patients with other types of cancer overexpressing PD-L1.³⁴⁹ Similarly, a clinician commented that pembrolizumab showed efficacy in patients expressing PD-L1 in more than 50% of tumor cells. However, this expert also noted that even patients with low levels of PD-L1 would benefit from pembrolizumab more than chemotherapy. Therefore, the potential of checkpoint inhibitors to fulfill the unmet need would be large if there were no cutoff in PD-L1 expression.³⁵⁹ Although one expert thought nivolumab does not have strong potential to improve outcomes, based on the available data, others thought the results from CheckMate 017, which was stopped early due to a survival advantage, would demonstrate nivolumab's potential to address an unmet need.³⁵⁰⁻³⁵³ Four experts thought survival and response data of pembrolizumab gave it a large potential to improve health outcomes.³⁵⁷⁻³⁶⁰ Despite the promising overall-survival rates, a health systems expert was concerned about comorbidities nivolumab may cause.³⁵⁴

Acceptance and adoption: Most experts concurred that physicians and patients would readily adopt nivolumab and pembrolizumab for treating NSCLC because of their potential to extend survival and their routine administration route. Severe adverse events could be a barrier for acceptance, opined an expert,³⁴⁹ although another pair of experts argued the survival benefits could outweigh adverse events and complications.^{354,359} Treatment with pembrolizumab requires tumors to have more than 50% of cells expressing PD-L1, which could cause patients and physicians to opt for nivolumab, which does not need assessment of PD-L1 levels, a clinician commented.³⁵⁹

Health care delivery infrastructure and patient management: Experts agreed that nivolumab and pembrolizumab would not disrupt treatment delivery or patient management. But if checkpoint inhibitors show a significant benefit, infrastructure would have to expand to accommodate more patients, an expert thought.³⁵¹ Nivolumab and pembrolizumab are given as an intravenous infusion, and experts concurred that health centers offering intravenous treatments already have the infrastructure to provide checkpoint inhibitors and that patient management would remain the same, and the drugs would simply be another offering.³⁵² Because of improved patient survival, however,

oncologists would need to monitor patients for a longer time for serious adverse events, an expert suggested.³⁵⁴ Testing for PD-L1 expression could possibly disrupt patient management because it may require taking biopsies and may delay pembrolizumab treatment, opined a clinician.³⁵⁹

Health disparities: Because NSCLC affects various patient populations, one clinician commenter did not anticipate that checkpoint inhibitors would affect health disparities.³⁵³ In contrast, six experts thought the very high prices of nivolumab and pembrolizumab could increase disparities in patients with low socioeconomic status.^{350,352,354,357,359,360} Additionally, people living in poverty have a higher exposure to smoking, asbestos, and air pollution, another expert noted.³⁵¹ Even if checkpoint inhibitors are covered by insurance, their high price of about \$136,500 per year will significantly increase health care costs, and copayments would be high. Five experts emphasized the fact that because lung cancer is the most common cancer, the cost burden would increase to third-party payers and patients.^{352-355,359}

Crizotinib (Xalkori) for Treatment of *ROS1*-Positive Nonsmall Cell Lung Cancer

Unmet need: Between 1% and 2% of NSCLC cases have an alteration in the *ROS1* proto-oncogene receptor tyrosine kinase that transforms cells and causes them to proliferate uncontrollably.³⁶¹ No drugs are approved for treating patients who have *ROS1* mutation–positive NSCLC. Crizotinib (Xalkori®) is a tyrosine kinase inhibitor FDA approved in 2011 for treating patients with NSCLC who are positive for *ALK* gene mutations.³⁶²⁻³⁶⁴ In patients with *ALK* mutation–positive NSCLC, crizotinib therapy improves progression-free survival compared with treatment with conventional cytotoxic chemotherapy.³⁶⁵ *ALK* and *ROS1* share 77% amino acid homology in their kinase domains, and crizotinib has antiproliferative effects in cell lines expressing constitutively active mutant forms of *ROS1*.^{361,366} Together, these observations suggest that crizotinib may also have activity in patients with *ROS1* mutation–positive NSCLC.

Intervention: *ROS1* mutation–positive NSCLC is a type of lung cancer that harbors a fusion between the *ROS1* gene and one of nine other genes: *SLC34A2*, *CD74*, *SDC4*, *EZR*, *KDEL2*, *CCDC6*, *TPM3*, *LRIG3*, or *FIG*. The *ROS1-CD74* fusion is the most common. Regardless of the fusion partner, the tyrosine kinase domain of *ROS1* remains intact and is thought to be constitutively active.³⁶¹ *ROS1* does not share fusion partners with *ALK*, which typically fuses with the *EML4* gene. Unlike *ALK-EML4* fusions, which form dimers and oligomers and have ligand-independent tyrosine kinase activity,^{363,364} *ROS1* fusions are not dimeric. The exact mechanism by which *ROS1* fusions lead to increased kinase activity is unknown. *ROS1* and *ALK* mutations do not usually occur concomitantly in patients with NSCLC.³⁶¹

Crizotinib acts as a tyrosine kinase inhibitor by competing with ATP for binding to *ALK* and *ROS1*, as well as to a third tyrosine kinase, c-MET/HGFR.³⁶⁵ Crizotinib treatment has been shown to improve clinical outcomes in patients with *ALK* mutation–positive NSCLC; however, a high percentage of patients experience disease relapse during the first year as the disease develops crizotinib resistance.^{363,364} This happens through mutations in the *ALK* kinase domain, which imparts inhibitor resistance; amplification of the *ALK* fusion gene, which causes cells to make more copies of *ALK* fusion protein; or activation of an alternative pathway that bypasses the need for *ALK* signaling.³⁶⁴ *ROS1* mutations have also been observed in patients with NSCLC after crizotinib treatment, as well as in vitro, suggesting that drug resistance may also arise in *ROS1* mutation–positive NSCLC.^{367,368}

Clinical trials: Crizotinib is being tested in phase I and phase II trials, alone and in combination with other investigational anticancer drugs. It is administered orally, at a twice-daily dosage of 250 mg. Dose reductions may be required in patients with renal impairment or in those who develop adverse reactions to the drug.³⁶² In an expansion cohort of the phase I PROFILE 1001 study, 50 patients with *ROS1*-positive NSCLC achieved a response rate of 72% (95% CI, 58 to 84) after receiving treatment, which resulted in 3 complete responses and 33 partial responses. After receiving crizotinib, patients also showed favorable duration of response (17.6 months; 95% CI, 14.5 to not reached) and progression-free survival (19.2 months; 95% CI, 14.4 to not reached).³⁶⁶ Similarly, in a retrospective study from the non-U.S. trial EUROS1, a cohort of 32 patients with *ROS1*-positive NSCLC also responded well to crizotinib treatment. The median progression-free survival was 9.1 months with a 44% progression-free survival rate at 12 months. The overall response rate was 80% and disease control rate was 86.7%, in which 2 patients had stable disease and 5 had complete responses.³⁶⁹

Interim analysis of safety data from an ongoing phase I trial in patients with *ROS1*-positive NSCLC indicate that adverse events are similar to those observed in patients with *ALK*-positive

NSCLC; these include vision disorder, nausea, diarrhea, vomiting, edema, and constipation.^{362,366} The prescribing information also lists the following warnings and precautions:³⁶²

- **Hepatotoxicity:** Drug-induced hepatotoxicity with fatal outcome has occurred. Monitor monthly and as clinically indicated with more frequent testing in patients with Grade 2-4 elevations. Temporarily suspend, dose reduce, or permanently discontinue XALKORI as indicated.
- **Pneumonitis:** Severe, including fatal, treatment-related pneumonitis has been observed. Monitor patients for pulmonary symptoms indicative of pneumonitis. Permanently discontinue in patients diagnosed with treatment-related pneumonitis.
- **QT Interval Prolongation:** In patients who have a history of or predisposition for QTc prolongation, or who are taking medications that are known to prolong the QT interval, consider periodic monitoring with electrocardiograms and electrolytes.
- **ALK Testing:** Detection of ALK-positive NSCLC using an FDA approved test, indicated for this use, is necessary for selection of patients for treatment with XALKORI.
- **Pregnancy:** XALKORI can cause fetal harm when administered to a pregnant woman.

Manufacturer and regulatory status: Crizotinib is manufactured by Pfizer, Inc. (New York, NY). In August 2011, FDA approved the drug for patients with locally advanced or metastatic *ALK*-positive NSCLC.³⁷⁰ In December 2015, FDA granted priority review for crizotinib, having previously granted breakthrough therapy status in April 2015 for treating *ROS1*-positive NSCLC;^{371,372} phase I and phase II trials for this indication are ongoing.

Diffusion and cost: As of September 2015, crizotinib reportedly cost about \$13,700 for 30 days of therapy (sixty 250-mg capsules).³⁷³ The manufacturer has established a program to provide financial assistance to uninsured and underinsured patients who require crizotinib treatment.²³

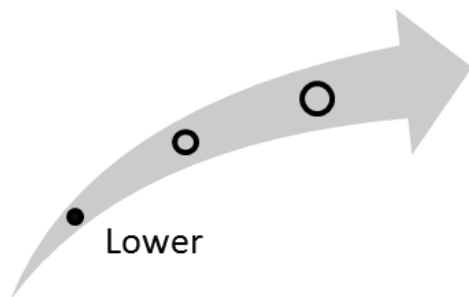
CMS has not issued a national coverage determination for crizotinib. The drug is a specialty pharmaceutical on some Medicare Part D plan formularies. Our searches of 11 representative, private, third-party payers that publish their policies online found all 11 have policies regarding crizotinib coverage for treating *ALK*-positive NSCLC; generally, prior authorization and quantity limits apply, and patients must have documented *ALK*-positive NSCLC.³⁷⁴⁻³⁸⁴ Four payers have established coverage policies for off-label crizotinib for treating *ROS1*-positive NSCLC. If crizotinib is approved for this indication, additional third-party payers are expected to adopt coverage policies.

Clinical Pathway at Point of This Intervention

Treatment of metastatic/unresectable NSCLC involves various systemic therapies. For the majority of patients, this consists of cytotoxic chemotherapy, typically beginning with platinum-based doublets in the first-line setting. However, for patients whose disease harbors identifiable and targetable driver mutations (e.g., *EGFR* mutations, *ALK* mutations), the preferred first-line treatment involves use of the appropriate targeted therapy. *ROS1* mutations represent another potentially actionable driver mutation in NSCLC.³⁸⁵ Like *EGFR* inhibitors and *ALK* inhibitors in *EGFR* mutation-positive and *ALK* mutation-positive NSCLC, crizotinib could become the preferred first-line therapy for patients with *ROS1*-positive NSCLC. Besides crizotinib, multiple second-generation *ALK/ROS1* inhibitors are being developed, including the recently FDA-approved inhibitor ceritinib. Ceritinib is being tested in two phase II trials in patients with *ROS1*-positive NSCLC and could potentially compete with crizotinib or be used in treating patients who develop crizotinib resistance.^{386,387}

Because activating *ROS1* mutations occur in a small fraction of NSCLC cases, performing a diagnostic test to detect *ROS1* gene fusions and to determine eligibility for crizotinib treatment is needed. FDA has approved two companion diagnostic tests based on fluorescent in situ hybridization (FISH) for detecting *ALK* gene fusions in NSCLC tumor samples.^{388,389} Although no such tests have FDA approval for diagnosing *ROS1*-positive NSCLC, at least one national diagnostic laboratory offers a commercially available FISH test (Aquarius® ROS1 breakapart FISH kit, CytoCELL Ltd., Cambridge, United Kingdom)³⁹⁰ for detecting *ROS1* gene fusions in NSCLC tumor samples.³⁹¹ Additionally, *ROS1* gene fusions are detectable by genetic sequencing methods. Increasing numbers of potentially actionable genetic mutations have been found in NSCLC, including well-established mutations (e.g., *EGFR*, *ALK*) and emerging mutations (e.g., *BRAF*, *HER2*, *RET*, *ROS1*). Given the numbers of mutations, National Comprehensive Cancer Network (NCCN) guidelines recommend that patients undergo multiplex testing with the potential to identify a number of mutations with a single test.³⁸⁵ Multiple, commercially available laboratory-developed tests are available for such testing.

Figure 11. Overall high-impact potential: crizotinib (Xalkori) for treatment of *ROS1*-positive nonsmall cell lung cancer



Most experts commenting on crizotinib concluded it has potential to benefit patients with *ROS1*-positive NSCLC, noting that its high efficacy and low toxicity will allow patients to have extended lives without affecting their quality of life. A clinician noted crizotinib falls within the most recent oncology model for targeted therapies, which involves developing highly effective treatments for a small number of patients. In contrast, based on poor outcomes in patients with NSCLC, an expert with a research perspective did not think crizotinib has much potential to fulfill the unmet need. The experts noted crizotinib is an oral drug for treating a small number of patients, and data from clinical trials have demonstrated it to be safe and effective; thus, they thought, crizotinib will face no barriers for acceptance and will be unlikely to affect health care delivery or patient management unless diagnostic testing becomes a limiting factor for patient access to crizotinib. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.³⁹²⁻³⁹⁷ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Although the number of patients with *ROS1*-positive NSCLC is relatively small part of the whole lung cancer population, survival rates are very poor because the disease does not respond to chemotherapy and the field lacks targeted therapies. Therefore, a need exists for patients with NSCLC bearing *ROS1* mutations. Most experts agree crizotinib has a potential to fulfill the unmet need in this patient population. Patients treated with

crizotinib had noticeable response to treatment and were disease-free for longer periods. In comparison to patients treated with a second-generation ALK inhibitor (ceritinib), patients treated with crizotinib manifested fewer adverse events.

Acceptance and adoption: Because crizotinib has shown efficacy in clinical trials and because of its safe profile, all experts agreed both physicians and patients will adopt crizotinib for treating *ROS1*-positive NSCLC. Two clinicians noted oncologists are beginning to treat patients with crizotinib, which has been thanks to their testing for alterations in *ROS1*, *EGFR*, and *ALK* on a regular basis.^{396,397} Another expert also argued in favor of crizotinib, because as an oral drug it will not require additional training and patients will be very excited about a targeted therapy that is more tolerable than standard chemotherapy.³⁹²

Health care delivery infrastructure and patient management: Overall, crizotinib is anticipated to affect neither health care delivery infrastructure nor patient management, experts concurred. Physicians will prescribe crizotinib to patients who are already receiving other oral targeted therapies. An aspect that may disrupt infrastructure and management could be the need for additional biopsies and facilities to detect targeted oncogenic mutations, a clinician commented.³⁹⁷

Health disparities: For the most part, experts do not anticipate crizotinib will affect health disparities. Although the high cost of crizotinib may impede uninsured and underinsured patients from having access to it, the small number of patients with *ROS1*-positive disease could limit the financial burden to patients and the health care system, expressed a clinician.³⁹⁶ Another expert with experience assessing health technologies thought the need for diagnostic testing to identify *ROS1* mutations could create disparities because patients with low socioeconomic status and low health literacy may not have access to centers that offer diagnostic testing.³⁹²

Next Generation EGFR Inhibitors (Osimertinib [Tagrisso], Rociletinib) for Treatment of Nonsmall Cell Lung Cancer

Unmet need: About 15% to 30% of NSCLC cases harbor an activating mutation in the gene encoding the epidermal growth factor receptor (EGFR), with higher rates in Asians, women and never smokers. EGFR inhibitors have improved outcomes for patients with *EGFR* mutation–positive NSCLC relative to cytotoxic chemotherapy; however, these inhibitors have limitations. First, NSCLC frequently develops resistance to EGFR inhibitors. This resistance is mediated in over half of all cases by a mutation in *EGFR* (T790M) that renders the encoded kinase insensitive to available inhibitors. Second, available EGFR inhibitors have activity against wild-type EGFR (i.e., nonmutated EGFR) in addition to mutant forms, and inhibiting wild-type EGFR in noncancer cells can lead to substantial toxicity.³⁹⁸ Substantial interest exists in developing next-generation EGFR inhibitors that have activity against resistant forms of EGFR (in particular T790M) and that are selective for oncogenic EGFR.

Intervention: Osimertinib (Tagrisso[™]) and rociletinib (formerly CO-1686) are two next-generation EGFR inhibitors under study for treating patients with *EGFR* mutation–positive NSCLC. Both drugs are small molecules that irreversibly inhibit EGFR, forming a covalent bond with a cysteine residue in the ATP-binding pocket of the kinase. Both drugs are highly selective for mutant forms of EGFR compared with wild-type EGFR, potentially inhibiting the oncogenic activity of mutated EGFR while sparing the activity of normal EGFR. Lastly, both drugs have demonstrated inhibition of EGFR isoforms that have acquired the secondary resistance mutation T790M. Because of these characteristics, investigators purport that these drugs could do the following:³⁹⁸⁻⁴⁰⁰

- Demonstrate activity in NSCLC resistant to available EGFR inhibitors (particularly NSCLC with a T790M mutation)
- Delay the emergence of EGFR inhibitor–resistant NSCLC if used in the first-line setting
- Improve tolerability relative to available EGFR inhibitors

Both drugs are orally administered and, like available EGFR inhibitors, are intended to be taken on an ongoing basis until disease progression.⁴⁰¹ Early clinical trials of the drugs used various dosages; however, ongoing late phase studies are using a dose of 80 mg once daily for osimertinib and 500 mg twice daily for rociletinib.^{402,403}

When used in treating patients who have the T790M resistance mutation confirmed, additional genetic testing may be needed. The T790M mutation is rarely present at baseline and typically emerges after treatment with an EGFR inhibitor.⁴⁰⁴ However, not all EGFR inhibitor–resistant NSCLCs harbor the T790M mutation; therefore, physicians will need to again biopsy a patient's cancer to determine the mechanism of resistance to initial EGFR therapy and potential eligibility for osimertinib or rociletinib treatment. Although upfront genetic testing to determine eligibility for targeted therapies (e.g., EGFR inhibitors, ALK inhibitors) has become standard of care, the practice of repeat genetic testing to determine resistance mechanisms is less widely adopted.⁴⁰⁵ The availability of therapies that could alter treatment choice based the information provided by repeat biopsies could drive wider adoption of this practice.^{398,406} Also, demand for repeat biopsies could promote the development and validation of less invasive biopsy methods, such as “liquid biopsy” methods based on circulating tumor cells or tumor-derived nucleic acids present in trace amounts in the bloodstream.^{406,407}

Clinical trials: For osimertinib, investigators have reported preliminary data from two single-arm trials (AURA and AURA2). In the phase I, dose-escalation phase of the AURA trial (n=127), osimertinib produced an overall response rate of 61% and a median progression-free survival of 9.6 months among patients with *EGFR* mutation–positive NSCLC who had undergone at least one prior

EGFR-inhibitor treatment and whose disease was confirmed to harbor the T790M resistance mutation.⁴⁰⁸ Additional T790M mutation–positive patients were enrolled in a phase II extension of the AURA trial and in the phase II AURA2 trial. In both trials all patients received treatment with osimertinib (80 mg once daily), and investigators reported response rates of 58% (115/199) and 64% (127/198) in the AURA extension cohort and AURA2 trials, respectively.^{409,410} The most common adverse events reported among patients receiving osimertinib included diarrhea, rash, dry skin, and nail toxicity.⁴¹¹ Frequency and severity of diarrhea and rash were reduced compared those historically observed with non-elective EGFR inhibitors.³⁹⁸ Osimertinib’s prescribing information also carries warnings about the potential for interstitial lung disease/pneumonitis, QTc interval prolongation, or cardiomyopathy to develop.⁴¹¹

A number of phase III trials testing osimertinib in various treatment settings are ongoing including the AURA3 trial comparing osimertinib to platinum-based chemotherapy in the second-line setting and the FLAURA trial comparing osimertinib to first-generation EGFR inhibitors (i.e., erlotinib, gefitinib) in the first-line setting.⁴¹² Also, the phase III CAURAL trial is studying the combination of the investigational immune checkpoint inhibitor durvalumab and osimertinib in treating patients with NSCLC previously treated with an EGFR inhibitor and harboring the T790M resistance mutation; however, patient enrollment in trials testing this combination was temporarily halted in the second half of 2015 because of reports of interstitial lung disease in patients receiving both drugs.^{412,413}

For rociletinib, investigators have published preliminary data from the phase I/II TIGER-X trial in which all patients received treatment with rociletinib. Among evaluable patients (n=46) with *EGFR* mutation–positive NSCLC who had undergone at least one prior EGFR-inhibitor treatment and whose disease was confirmed to harbor the T790M resistance mutation, investigators reported an overall response rate of 59% and a median progression-free survival of 13.1 months.⁴⁰¹ However, subsequent reports from this trial including more patients and longer followup have reported lower response rates.^{414,415}

The most common adverse events reported among patients (n=92) receiving therapeutic doses of rociletinib in the TIGER-X trial were hyperglycemia (47%), nausea (35%), fatigue (24%), diarrhea (22%), and decreased appetite (20%). Frequency and severity of diarrhea was reduced compared to those observed with nonselective EGFR inhibitors, and few cases of rash were observed.^{398,401} To address hyperglycemia, 38% of patients required treatment with a glucose-lowering drug (typically metformin).⁴⁰¹

Two phase III trials of rociletinib are ongoing. In the TIGER-1 trial, rociletinib is being compared head-to-head with erlotinib in patients with *EGFR* mutation–positive NSCLC not previously treated with an EGFR inhibitor.⁴¹⁶ In the TIGER-2 trial, rociletinib is being studied in patients with *EGFR* mutation–positive NSCLC who have previously been treated with both an EGFR inhibitor and platinum-based chemotherapy.⁴⁰³

Manufacturer and regulatory status: Osimertinib is being developed by AstraZeneca (London, UK). In November 2015, FDA granted accelerated approval to osimertinib for treating NSCLC in “patients whose tumors have a specific *epidermal growth factor receptor (EGFR)* mutation (T790M) and whose disease has gotten worse after treatment with other EGFR-blocking therapy.”⁴¹⁷ The new drug application for osimertinib was reviewed under the agency’s priority review program, and the agency had previously granted osimertinib orphan drug and breakthrough therapy designations.⁴¹⁸ Use in patients harboring the T790M resistance mutation will require using a diagnostic test to determine T790M mutation status. At the time of osimertinib’s approval, FDA also approved a premarket application for a companion diagnostic test for osimertinib, the cobas *EGFR* mutation test v2 (F. Hoffmann-La Roche, Ltd., Basel, Switzerland).⁴¹⁷

Rociletinib is being developed by Clovis Oncology (Boulder, CO). In August 2015, Clovis announced it had completed a new drug application filing for rociletinib with FDA, seeking accelerated approval for treating patients who have *EGFR* mutation–positive NSCLC that has been treated with an *EGFR*-targeted therapy and has the *EGFR*^{T790M} mutation.⁴¹⁹ FDA has granted the application priority review status, and a decision deadline is set for March 2016.⁴²⁰ However, in November 2015, Clovis announced that FDA had requested additional data on rociletinib, which could delay a decision on approval.⁴¹⁵ FDA had previously granted rociletinib breakthrough therapy status.⁴²¹ Clovis has formed a partnership with QIAGEN, N.V. (Venlo, the Netherlands), to develop a companion diagnostic test for rociletinib. Clovis has indicated that QIAGEN intends to file a supplementary premarket approval application with FDA for its therascreen *EGFR* test, which FDA has already approved as a companion diagnostic for the *EGFR* inhibitor afatinib.⁴²² Also, Clovis is reportedly testing a blood-based genotyping method based on technology from Sysmex Corp. (Kobe, Japan); however, a timeline for potential regulatory approval of a companion diagnostic based on this technology has not been established.⁴¹⁴

Diffusion and cost: After osimertinib's approval in November 2015, AstraZeneca announced that the drug would be available at a wholesale acquisition cost of \$12,750 per month.⁴²³ If rociletinib is approved by FDA, it is likely that the drug would be priced comparably. Besides the direct drug costs associated with osimertinib and rociletinib, patients may require testing for the T790M mutation to be eligible for treatment. This would lead to additional costs associated with secondary biopsy and genetic testing procedures.

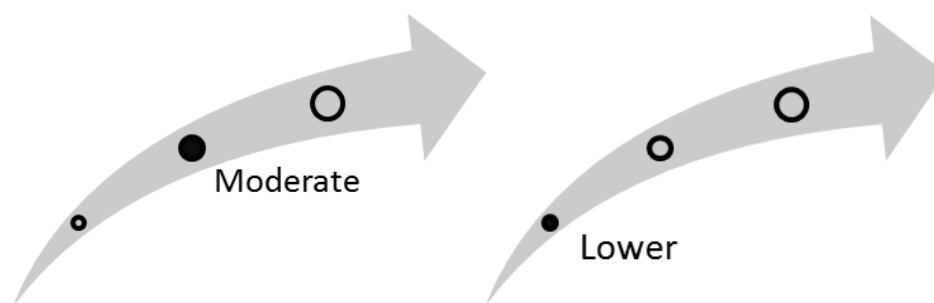
Clinical Pathway at Point of This Intervention

Osimertinib and rociletinib are under study for treating patients who have metastatic or unresectable, *EGFR* mutation–positive NSCLC. According to National Comprehensive Cancer Network (NCCN) guidelines for treating NSCLC, an *EGFR* inhibitor (either erlotinib or afatinib) is the standard first-line treatment for patients with sensitizing *EGFR* mutations. *EGFR* inhibitors are taken on an ongoing basis until disease progression. Patients with unifocal progression or progression in the brain only may continue *EGFR*-inhibitor therapy in conjunction with local therapy.³⁸⁵

For patients with symptomatic, multifocal disease progression during *EGFR* inhibitor treatment, NCCN recommends one of several cytotoxic chemotherapy regimens, the choice of which depends on tumor histology (i.e., nonsquamous vs. squamous) and patient performance status. Patients with good performance status typically receive doublet chemotherapy consisting of a platinum agent (i.e., cisplatin, carboplatin) and a second agent (e.g., docetaxel, gemcitabine, paclitaxel, pemetrexed). Also, nonsquamous NSCLC may be treated by adding the anti-VEGF-A monoclonal antibody bevacizumab to standard doublet chemotherapy.³⁸⁵

Subsequent therapy after initial platinum-based chemotherapy has historically consisted of additional cytotoxic regimens, frequently monotherapies such as docetaxel, gemcitabine, paclitaxel, or pemetrexed. However, more recently, immunotherapy approaches, in particular agents targeting the PD-1 immune checkpoint, have been introduced for treating patients who have NSCLC. The NCCN guidelines include the PD-1 inhibitor nivolumab as an additional treatment option for subsequent therapy in patients experiencing disease progression after initial cytotoxic chemotherapy.³⁸⁵

Figure 12. Overall high-impact potential: next-generation EGFR inhibitors (osimertinib [Tagrisso]), rociletinib) for treatment of nonsmall cell lung cancer



Overall, experts suggested that osimertinib and rociletinib has demonstrated substantial promise in treating patients with T790M mutation-positive NSCLC, a population for which an active targeted therapy has long been sought. Based on these promising results, the majority of commenters suggested that the drugs would be widely adopted; however, they also cautioned that long-term studies comparing the drugs to standard care would be needed to confirm the clinical benefit. As oral capsules, the drugs would not require substantial disruption to health care facility staffing, infrastructure, or patient management other than repeat biopsies and additional genetic testing used to determine T790M mutation status, according to some commenters. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on osimertinib⁴²⁴⁻⁴²⁹ and six experts, with similar backgrounds, offered perspectives on rociletinib.⁴³⁰⁻⁴³⁵ Two of the reviewers, one with a clinical perspective and the other with a research perspective, provided comments on both topics.^{427,428,433,434} We have organized the following discussion of expert comments according to the parameters on which they commented. It should be noted that expert comments made their comments before FDA approved osimertinib in November 2015.

Unmet need and health outcomes: The magnitude of the unmet need potentially addressed by the next generation EGFR inhibitors osimertinib and rociletinib is moderate to high according to the majority of experts commenting. They cited as factors the frequency and rapidity with which resistance to first- and second-generation inhibitors typically develops and the substantial toxicity associated with first- and second-generation EGFR inhibitors. While the unmet need was seen as acute for patients eligible for osimertinib or rociletinib treatment, several commenters observed that their potential impact was limited by the relatively small number of eligible patients relative to the overall size of the health care landscape. Also, multiple commenters noted that alternative treatment options such as cytotoxic chemotherapy and immune checkpoint inhibitors exist for these patients. Despite these treatment alternatives, most commenters suggested that the lack of EGFR-targeting drugs with activity against T790M mutated NSCLC, represents an important unmet need.

Experts commenting on osimertinib suggested that the overall response rates reported in the AURA and AURA2 clinical trials were promising evidence of clinical activity in patients with T790M-mutation positive NSCLC whose disease had progressed following EGFR targeted therapy. Two experts with clinical perspectives indicated that response rates reported for osimertinib are substantially higher than those historically observed for chemotherapy in this patient population and suggested that osimertinib has a large potential to improve patient health outcomes. Osimertinib's tolerability profile was also assessed by these commenters as more favorable than alternatives in this setting, further enhancing the drug's potential to improve patient health. Conversely, experts with research perspectives were more cautious in their opinion of osimertinib's potential to improve

patient health. These experts noted that, although the reported response rates were promising, the only available trial data were from single-arm trials lacking comparator arms; that data were restricted to overall response rate and progression-free survival, which might not translate to improved overall survival; and that ongoing studies need to be completed to make a full assessment of osimertinib's potential. Although most of the comments focused on patients with T790M mutation-positive NSCLC, one expert with a clinical perspective also suggested that osimertinib could have some clinical use in patients previously treated with an EGFR inhibitor but lacking the T790M mutation. Although reported response rates for osimertinib in T790M mutation–negative disease were lower than those reported for T790M mutation–positive disease, according to this commenter, the response rate in T790M mutation–negative disease was comparable to the historical response rate for cytotoxic chemotherapy in this setting.

Expert comments on the potential of rociletinib to improve patient health were consistent with those received for osimertinib; however, it should be noted that these comments were solicited before the recent revision to response rates released by Clovis Oncology in November 2015.⁴¹⁵

Acceptance and adoption: Osimertinib and rociletinib would likely be moderately to widely adopted according to a majority of commenters. These commenters suggested that the promising preliminary evidence for the safety and efficacy of the two drugs and lack of highly effective therapies for the intended patient population would be the main drivers of adoption. However, these commenters also cautioned that these results need to be confirmed in larger trials incorporating comparator arms. Indeed, one expert with a research perspective suggested that only minimal adoption was likely given the preliminary nature of the data.⁴²⁴ Patient preference for oral, rather than infused drugs, was also seen by some experts as a factor that would promote adoption.^{425,429} Conversely, one commenter speaking from a clinical perspective noted that the requirement for repeat biopsy to determine T790M status would require additional clinician education and that the morbidity associated with invasive biopsy could dissuade some patients from opting for osimertinib or rociletinib treatment; however, this commenter still envisioned wide adoption of the drugs.^{427,434}

Health care delivery infrastructure and patient management: Because these drugs are administered orally, the majority of commenters envisioned only minimal changes to health care facility infrastructure and patient management. Several of these commenters suggested that switching from intravenous chemotherapy to oral targeted therapy represents a small shift in patient management. Commenters thought the biggest change in care would be the need for additional biopsies to determine eligibility for the drugs. In particular, one commenter with a clinical perspective indicated that this practice could place pressure on already heavily burdened interventional radiology and pulmonary services, which perform the lung tissue biopsies.^{427,434}

Health disparities: These drugs would not improve health disparities, thought experts commenting. Several commenters noted that these drugs were likely to be another expensive oncology treatment and, therefore, could exacerbate any existing disparities caused by socioeconomic status. Also, multiple commenters noted that the requirement for and costs associated with a second round of biopsies and genetic testing to identify T790M mutation status could also widen existing disparities. Lastly, one expert with a clinical perspective suggested that, because these drugs are orally administered, patients could be responsible for larger copayments than they would for an infused therapy, again potentially further widening disparities based on the ability to pay.⁴²⁹

Neuroblastoma Intervention

Dinutuximab (Unituxin) for Treatment of Neuroblastoma

Unmet need: Although pediatric overall survival rates for neuroblastoma have increased, many pediatric patients in whom aggressive or advanced disease is diagnosed have high rates of recurrence and a poor prognosis. A majority of these patients have metastatic disease at the time of diagnosis. Improved therapeutic options are needed, particularly for those with high-risk disease or who experience disease recurrence after remission.^{436,437} A potential new immunotherapy for treating neuroblastoma targets disialoganglioside (GD2), a glycolipid expressed on the surface of neuroblastoma cells. GD2 is uniformly expressed in neuroblastoma cells, but its expression in normal tissue is limited to neurons, peripheral nerve fibers, and skin melanocytes.⁴³⁸ Because of this favorable expression profile, treatment with a recently approved monoclonal anti-GD2 antibody called dinutuximab (UnituxinTM) may be a promising addition to therapies for neuroblastoma.

Intervention: The choice of which first-line therapy to use in treating neuroblastoma depends on a patient's risk stratification per the Children's Oncology Group classification.⁴³⁹ Patients with high-risk neuroblastoma that has metastasized to bone and bone marrow typically undergo a regimen of intensive induction chemotherapy followed by myeloablative consolidation chemotherapy and autologous stem cell transplantation. Surgical resection and localized radiation therapy may also be used for local tumor control.^{436,439,440} As the final part of the therapeutic regimen for high-risk neuroblastomas, retinoic acid analogues and investigational agents are often used to treat minimal residual disease and to try to prevent recurrence.^{436,439} One such investigational agent is the monoclonal antibody dinutuximab.

Dinutuximab is an antibody specific for GD2, a glycolipid found on the surface of certain tumor cells, including neuroblastomas.⁴⁴¹ In normal tissue, GD2 expression is restricted to neurons, skin melanocytes, and peripheral sensory nerve fibers. Binding of dinutuximab to GD2 on tumor cells is thought to trigger cell death through complement-dependent cytotoxicity and/or antibody-dependent cellular cytotoxicity. Also, high GD2 levels on the cell surface of neuroblastomas are thought to facilitate the interaction of tumor cells with extracellular matrix. Therefore, besides generating passive immunity to neuroblastomas, dinutuximab binding may also prevent circulating tumor cells from adhering to the extracellular matrix, an important aspect in the process of tumor metastasis.⁴³⁷

Dinutuximab is a chimeric antibody with both human and murine components; it combines regions of murine immunoglobulin G3 anti-GD2 with the constant regions of human immunoglobulin G1-gamma.⁴⁴² This chimeric form was designed to avoid human anti-mouse antibody reactions during which the body develops antibodies to murine-based antibodies, neutralizing the immunotherapy.^{443,444} Compared with murine anti-GD2 antibody (i.e., 3F8 and 14G2a), dinutuximab has significantly greater potency and reduced immunogenicity.^{437,444}

In U.S. clinical trials that supported a new drug application, dinutuximab was administered at an IV dose of 25 mg/m² for 4 consecutive days during 5 consecutive 4-week cycles, followed by 1 cycle of rest.^{445,446}

Clinical trials: In the phase III ANBL0032 trial, patients with high-risk neuroblastoma who were treated with induction therapy and stem-cell transplantation and had at least a partial response were randomly assigned in a 1:1 ratio to receive standard therapy (6 cycles of oral isotretinoin, 160 mg/mg² for 14 days of a 28-day cycle) or standard therapy plus immunotherapy (5 cycles of intravenous dinutuximab, 25 mg/mg² for 4 days of a 28-day cycle in combination with interleukin-2 (IL-2) and granulocyte-macrophage colony-stimulating factor (GM-CSF). In 2010, Yu and colleagues reported safety and efficacy of dinutuximab in 226 patients in the trial in which the primary endpoint was event-free survival, defined as a relapse, progressive disease, secondary malignancy, or death. At 2 years, patients treated with immunotherapy had superior event-free

survival rates compared to standard care, ($66\pm 5\%$ vs. $46\pm 5\%$; $p=0.01$) and overall survival ($86\pm 4\%$ vs. $75\pm 5\%$; $p=0.02$). Despite improved outcomes, immunotherapy was associated with a higher rate of grade 3, 4, or 5 adverse events. Pain (52%), hypersensitivity reactions (25%), and capillary leak syndrome (23%) were rare toxic events that required monitoring. Additional adverse events more commonly associated with immunotherapy included hypokalemia (35%), hyponatremia (23%), liver dysfunction (23%), hypotension (18%), diarrhea (13%), urticaria (13%), and hypoxia (13%).⁴³⁸

At the 2014 European Society for Medical Oncology conference, investigators presented additional safety and efficacy results from 105 patients enrolled in the phase III ANBL0032 trial whose treatment with dinutuximab was extended from 5.72 hours to 10 hours per infusion. Although rates for event-free survival ($86\pm 4\%$) and overall survival ($75\pm 5\%$) were similar to what was reported previously, immunotherapy-related toxicities were less prevalent and could be associated with duration of infusion, including pain (cycles 1, 2, 3, 4, and 5 were 30.9%, 22%, 13.3%, 20%, and 17%, respectively), hypersensitivity (2.9%, 9%, 3%, 6.6%, 2.2%), and capillary leak syndrome (1%, 4%, 0%, 2.2%, 0%).⁴⁴⁷

Manufacturer and regulatory status: In the United States, dinutuximab was developed and tested by the Children's Oncology Group, (Monrovia, CA) an international, multicenter clinical trials group funded by the National Cancer Institute (NCI). In July 2010, United Therapeutics Corp. (Silver Spring, MD) entered into a cooperative research and development agreement (commonly known as a CRADA) with NCI for late-stage development and regulatory submissions for dinutuximab.⁴⁴¹ Under the agreement with NCI, United Therapeutics is also performing a comparative pharmacokinetic study to ensure consistency between the pharmacokinetic profiles of dinutuximab manufactured by NCI and United Therapeutics.⁴⁴⁸

In March 2015, basing its decision on data from the phase III ANBL0032 trial, FDA approved dinutuximab in combination with GM-CSF and IL-2 for treating high-risk neuroblastoma in pediatric patients with at least a partial response to first-line multimodal therapy.⁴⁴⁹

In the European Union, APEIRON Biologics AG (Vienna, Austria) is collaborating with the International Society of Paediatric Oncology European Neuroblastoma (SIOPEN) for dinutuximab's clinical development.⁴⁵⁰ BioInvent International AB (Lund, Sweden) also produces an antibody against GD2, which was tested in the Cooperative German Neuroblastoma Trials (NB90 and NB97).⁴⁵¹

Diffusion and cost: Because of the limited commercial availability of dinutuximab, pricing information is not yet available. However, its cost may be inferred from the price of similar monoclonal antibodies. Bevacizumab, a monoclonal antibody specific against VEGF, which is approved for treating breast cancer, cervical cancer, colorectal cancer, glioblastoma, kidney cancer, and lung cancer, may be a useful pricing benchmark.^{452,453} As of December 2014, the retail price of bevacizumab was about \$5,600 for 2 vials with 400 mg each. A patient of average weight (70 kg) would receive about 700 mg (10 mg/kg) of bevacizumab once every 2 weeks, which equates to about \$4,900 per treatment cycle or \$127,400 per year.⁴⁵⁴

Clinical Pathway at Point of This Intervention

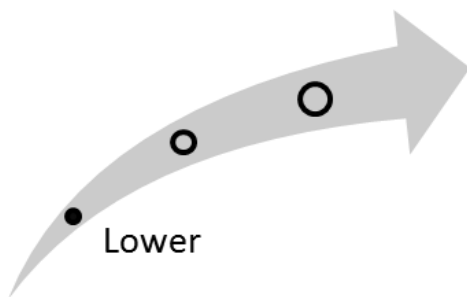
Maintenance therapy is used to treat minimal residual disease and prevent recurrence after a standard regimen of induction therapy, consolidation therapy, and stem cell transplantation. Several agents are under investigation for providing maintenance therapy.

Numerous other GD2-targeted antibodies have been developed, but dinutuximab immunotherapy is the furthest along in development. The others are the focus of ongoing or previous clinical trials, but are not available commercially. First-generation murine monoclonal anti-GD2 antibodies include 14G2a and 3F8.^{437,442}

Other agents are also under study. To prevent human anti-mouse antibody reactions, second-generation humanized forms of GD2 monoclonal antibodies were developed; these include Hu14.18K332A, the cytokine-antibody conjugate Hu14.18-IL-2, and the anti-idiotypic antibody 1A7.^{437,442} Besides GD2-targeted therapies, radiopharmaceutical agents are also under investigation. Ninety percent of neuroblastoma cells have avidity for ¹³¹I-metaiodobenzylguanidine, a norepinephrine transporter–targeted radiotracer. This compound is also the focus of numerous early to mid-stage trials for treating neuroblastoma. Finally, about 10% of neuroblastomas harbor mutations in the gene encoding ALK, and early phase trials are also examining ALK-inhibitor efficacy in patients with *ALK* mutations.⁴⁴²

The cytokines GM-CSF and IL-2 are often co-administered with dinutuximab to enhance the antibody-dependent cellular cytotoxicity response in immunosuppressed patients after autologous stem cell transplantation.⁴³⁷ These agents increase the number of granulocytes, macrophages, and NK cells in patients with weakened immune systems to augment the immune response against antibody-labeled tumor cells.⁴³⁸ Also, because anti-GD2 antibody binding to normal tissues can result in acute pain and hypersensitivity reactions, pain medication, acetaminophen, and antihistamines may be administered before and during dinutuximab infusions.⁴³⁷

Figure 13. Overall high-impact potential: dinutuximab (Unituxin) for treatment of neuroblastoma



Despite the small number of patients who develop neuroblastoma each year, patient outcomes are very poor because most cases are metastatic at the time of diagnosis, and the disease has a high recurrence rate. Overall experts agreed dinutuximab has moderate potential to address the unmet need. Even with strong results showing survival surpassing 2 years, an expert thought further data are needed to assess patient quality of life.⁴⁵⁵ Meanwhile, another expert stated the efficacy of dinutuximab may be associated with its specificity for the neuroblastoma antigen GD2.⁴⁵⁶ Although additional data are needed, the available survival outcomes were sufficient for experts to suggest dinutuximab will be adopted by clinicians and patients without requiring additional health care infrastructure or affecting patient management. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on dinutuximab for treating neuroblastoma.⁴⁵⁵⁻⁴⁶⁰ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Although the 5-year survival rate is relatively high in pediatric patients with neuroblastoma because of the treatment options available (i.e., radiation, chemotherapy, surgery, stem cell transplantation), the recurrence rate is high, and many children still die because the disease has metastasized when initially diagnosed, experts noted. Thus, an important unmet need exists for patients with neuroblastoma. Most experts agreed dinutuximab has a moderate potential to improve patient health, basing their opinions on positive results from a trial

demonstrating dinutuximab increased patient survival, as compared with standard of care.^{455,457-459} However, efficacy of dinutuximab may be contingent on the patient being able to develop immunity against the neuroblastoma, a clinician opined.⁴⁶⁰

Acceptance and adoption: Experts unanimously agreed that both physicians and patients (i.e., their parents) would adopt the use of dinutuximab for treating neuroblastoma. It is a well-tolerated new option that has shown potential to extend survival. Two experts pointed out clinicians will need to closely monitor patients for dinutuximab-related adverse events, which could cause complications.^{458,459}

Health care delivery infrastructure and patient management: Similar to other systemic cancer treatments, dinutuximab is an IV drug and has little potential to disrupt delivery infrastructure and patient management, experts concurred. No disruption to the care pathway is anticipated, opined most experts. However, two experts thought adding dinutuximab to the standard of care would change the clinical pathway after stem cell transplantation somewhat.^{455,457}

Health disparities: Dinutuximab is not expected to affect disparities because neuroblastoma affects a small number of children regardless of their race and socioeconomic status, all experts agreed. Although the cost of dinutuximab is expected to be similar to other monoclonal antibodies, two experts pointed out dinutuximab will be an add-on to standard treatment and added costs could be a burden to the patient's family unless insurance offers reimbursement.^{458,459}

Skin Cancer Interventions

Checkpoint Inhibitors (Nivolumab [Opdivo], Pembrolizumab [Keytruda]) for Treatment of Advanced Melanoma

Unmet need: Despite recent advances in treatment options for melanoma, many patients in whom advanced melanoma has been diagnosed have a poor prognosis, and new treatments are needed. Recent phase III clinical trials with the anti-cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) monoclonal antibody, ipilimumab (Yervoy®), demonstrated the potential of immune checkpoint inhibitors to produce durable responses in patients with advanced melanoma by activating the body’s immune system.^{308,309} However, only a minority of patients experience such a response, and new approaches to stimulate immune responses to melanoma are highly sought. One approach targets the PD-1 receptor, a second immune checkpoint pathway that reportedly suppresses the anti-melanoma immune response. Several molecules targeting PD-1 or PD-1 ligands are under study in clinical trials for treating melanoma, including the PD-1–specific monoclonal antibodies nivolumab (Opdivo®) and pembrolizumab (Keytruda®).^{272,314,461}

Intervention: Evading destruction by the body’s immune system is a hallmark of cancer, and researchers have identified several mechanisms by which cancers induce immune tolerance.^{271,272} One such mechanism is the co-option by tumors of endogenous mechanisms that limit T-cell responses. These so-called immune checkpoints are thought to have evolved to prevent runaway immune responses; however, by aberrantly activating these immune checkpoints, cancers purportedly can reduce the body’s anticancer immune response.²⁷²

PD-1 is a central player in one of these checkpoints.²⁷² PD-1 is expressed by many cells of the immune system, including high expression levels on activated T cells. Research has demonstrated that in many cases, the tumor microenvironment expresses a ligand for PD-1 (PD-L1). Binding of PD-L1 to PD-1 is thought to induce T-cell anergy (diminished response to persistent antigen exposure), limiting tumor rejection by tumor-specific T cells in the effector phase of the immune response.²⁷³ Disrupting the immune tolerance–inducing signaling between tumor-expressed PD-L1 and immune cell–expressed PD-1 is a therapeutic target that could potentially induce an immune response to the cancer by “releasing a brake” cancer cells have placed on the immune response through the signaling pathway.²⁷²

Nivolumab is a fully humanized, immunoglobulin G4 monoclonal antibody highly specific for PD-1.²⁷⁵ Similarly, pembrolizumab is a humanized monoclonal antibody in which the Fc region has been modified to reduce antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity, which have the potential to deplete immune cells expressing PD-1.³¹⁴ Preclinical studies performed in animal cancer models have shown that antibody-mediated inhibition of the PD-1/PD-L1 pathway increases T-cell antitumor response.²⁷⁴ Nivolumab or pembrolizumab binding to PD-1 purportedly prevents the interaction between PD-1 and its ligands, preventing activation of the immune checkpoint and leading to an increase in anticancer immune response.²⁷⁴

Nivolumab and pembrolizumab are administered by IV infusion. In phase I trials, researchers tested escalating doses of nivolumab for various cancers, infusing doses ranging from 0.3 to 10 mg/kg.^{274,315} In ongoing phase III trials, patients with melanoma are given 3 mg/kg of nivolumab once every 2 weeks.³¹⁶⁻³¹⁹ Pembrolizumab, which FDA recently approved, has prescribing information recommending 2 mg/kg once every 3 weeks, and treatment may continue for up to 2 years.^{320,321}

Clinical trials: Nivolumab and pembrolizumab are being tested primarily as immunotherapy for advanced melanoma and NSCLC.^{276-281,317-320,462} Investigators have also initiated clinical trials of nivolumab and pembrolizumab for treating triple-negative breast cancer, head and neck cancer, urothelial tract cancer, gastric cancer, and blood cancers.^{274,315,463,464}

Nivolumab. In April 2015, results from the phase III CheckMate-037 trial were published, in which patients with metastatic melanoma whose disease had progressed after ipilimumab treatment were given nivolumab (n=120) or investigator's choice of chemotherapy (n=47). The objective response rate was compared between groups. An independent review committee reported that patients who were treated with 3 mg/kg nivolumab had a significantly higher objective response rate (32%; 95% CI, 24% to 41%) than patients who received chemotherapy (11%; 95% CI, 3.5% to 23%). Conversely, grade 3–4 adverse events were less frequent after treatment with nivolumab (5%) than after chemotherapy (9%).⁴⁶⁵

Nivolumab's efficacy in untreated patients with unresectable advanced melanoma bearing the wild-type *BRAF* gene was evaluated in the phase III CheckMate-066 trial (n=418). Authors published results in January 2015 reporting that after 1 year of treatment with nivolumab, overall survival and progression-free survival improved significantly compared with those outcomes in patients treated with dacarbazine. Overall survival in the nivolumab group was 73% (95% CI, 65% to 79%), and in the dacarbazine group, it was 42% (95% CI, 33% to 51%). The median progression-free survival in the nivolumab group was 5.1 months versus 2.2 months in the dacarbazine group (HR, 0.43; 95% CI, 0.34 to 0.56; p<0.001). Grade 3–4 adverse events occurred in 11.7% of patients treated with nivolumab and 17.6% of patients treated with dacarbazine. The most common nivolumab-related adverse events were fatigue, pruritus, and nausea.⁴⁶⁶ In June 2014, the manufacturer announced that the CheckMate 066 trial would be stopped and unblinded ahead of schedule because of a significant benefit observed in patients treated with nivolumab compared with dacarbazine. Patients receiving the latter treatment were offered nivolumab in an open-label extension of the study.⁴⁶⁷

Results were reported in May 2015 from CheckMate 067, a phase III, randomized, double-blind, controlled trial assessing the efficacy and safety of nivolumab as monotherapy or in combination with ipilimumab in treatment-naïve patients with unresectable, advanced melanoma. Nivolumab plus ipilimumab showed a superior clinical benefit over nivolumab or ipilimumab monotherapy. The median progression-free survival was 11.5 months in the nivolumab plus ipilimumab group (HR, 0.42; 99.5% CI, 0.31 to 0.57; p<0.001) and 6.9 months in the nivolumab group (HR, 0.57; 99.5% CI, 0.43 to 0.76; p<0.001), compared with 2.9 months in the ipilimumab group. However, a higher rate of grade 3 and 4 treatment-related adverse events were observed in patients who received nivolumab plus ipilimumab (55%) than in those treated with nivolumab (16%) or ipilimumab (27%) alone.⁴⁶⁸

Pembrolizumab. Results from KEYNOTE-001 were published in July 2013. Investigators in this phase I, open-label trial of 135 patients with advanced melanoma reported that a regimen of 10 mg/kg pembrolizumab administered every 2 weeks had the highest response rate (52%; 95% CI, 38% to 66%) relative to other dosages. No significant difference was observed in the response rate between patients who had previously received ipilimumab (38%; 95% CI, 23% to 55%) and those who had not (39%; 95% CI, 26% to 49%). The most common pembrolizumab-related adverse events included fatigue, rash, pruritus, and diarrhea; side effects were reported in 79% of patients. Of those experiencing side effects, 13% of patients experienced grade 3 or 4 adverse events.⁴⁶⁹

In April 2015, results from the phase III KEYNOTE-006 trial were published. In this open-label study, 834 patients with advanced melanoma were randomly assigned to 1 of 3 groups, in a 1:1:1 ratio, to receive IV pembrolizumab (10 mg/kg) every 2 weeks or every 3 weeks until disease progression, or 4 doses of IV ipilimumab (3 mg/kg) every 3 weeks. At 6 months, the progression-free survival rates after treatment with pembrolizumab were 47.3% for every 2 weeks and 46.4% for every 3 weeks, as compared with 26.5% for ipilimumab (HR, 0.58; 95% CI, 0.46 to 0.72 for 2 weeks of treatment and HR, 0.58; 95% CI, 0.47 to 0.72 for 3 weeks of treatment). Similarly, after 1 year, patients treated with pembrolizumab had a higher survival rate than patients treated with

ipilimumab, which were 74.1% for 2 weeks (HR, 0.63; 95% CI, 0.47 to 0.83; $p < 0.0005$) and 68.4% for 3 weeks (HR, 0.69; 95% CI, 0.52 to 0.90; $p < 0.0036$) when compared with 58.2% for ipilimumab. Patients who received ipilimumab experienced a higher rate of grade 3–5 treatment-related adverse events (19.9%) than patients receiving either pembrolizumab regimen (every 2 weeks, 13.3%; every 3 weeks, 10.1%).⁴⁷⁰ In March 2015, the manufacturer announced the phase III KEYNOTE-006 trial had met its coprimary endpoints of progression-free survival and overall survival. The trial was stopped early after an independent data monitoring committee confirmed that pembrolizumab improved overall and progression-free survival, as compared with ipilimumab.⁴⁷¹

Manufacturer and regulatory status: Nivolumab is being developed by Bristol-Myers Squibb (New York, NY). After granting priority review in September 2014, FDA approved nivolumab under its accelerated approval program in December 2014 for treating patients with advanced melanoma after treatment with ipilimumab or a BRAF inhibitor if patients have the *BRAF*^{V600} mutation.^{286,287} Basing its decision on results from the phase II CheckMate 069 trial demonstrating that nivolumab plus ipilimumab improved response rates (60% combination [95% CI, 48 to 71; $p < 0.001$] vs. 11% ipilimumab alone [95% CI, 3 to 25]), in October 2015, FDA also granted accelerated approval to nivolumab in combination with ipilimumab for treating unresectable metastatic melanoma that is *BRAF* wild-type.^{472,473} Also, FDA approved a supplemental biologics license application (sBLA) for nivolumab in the first-line setting for treating advanced melanoma *BRAF* wild-type. The decision was reached in November 2015 on the basis of results from the phase III CheckMate 066 trial.⁴⁷⁴ The company has also submitted an sBLA containing data from the phase III CheckMate 067 trial to FDA for nivolumab in the first-line setting for treating melanoma patients bearing *BRAF*^{V600} mutation. A decision is expected by January 2016.⁴⁷⁵ FDA also granted nivolumab fast-track status in 2013 for treating melanoma, NSCLC, and RCC, and in March 2015 it was approved for treating recurrent NSCLC.^{289,290}

Pembrolizumab is being developed by Merck & Co., Inc. (Whitehouse Station, NJ). In September 2014, FDA approved pembrolizumab for treating unresectable or metastatic melanoma in patients whose disease has progressed after treatment with ipilimumab or a BRAF inhibitor (if the patient had a confirmed *BRAF* gene mutation).⁴⁷⁶ Pembrolizumab was approved on the basis of tumor response rate and durability of response;^{476,477} in December 18, 2015, FDA granted full approval for treating patients with unresectable or metastatic melanoma and disease progression after ipilimumab and, if *BRAF*^{V600} mutation positive, a BRAF inhibitor. At the time of the accelerated approval process, improved survival or disease-related symptoms had not yet been established; however, in accordance with the accelerated approval process, FDA granted full approval upon verification of clinical benefit, which has now been demonstrated in the KEYNOTE-002 and KEYNOTE-006 trials.⁴⁷⁸ In December 2015, FDA also approved pembrolizumab as first-line therapy for treating unresectable or metastatic melanoma.⁴⁷⁸ FDA had earlier granted pembrolizumab breakthrough therapy status for treating advanced melanoma.⁴⁷⁹

Diffusion and cost: In the United States the cost of nivolumab is about \$2,500 for a 100 mg vial. Therefore, a single infusion for a 70 kg patient at the typical dose of 3 mg/kg would cost about \$5,250, which is about \$136,500 per year.³³⁵

As of May 2015, pembrolizumab costs about \$6,600 for 3 vials of 50 mg, which at a dose of 2 mg/kg every 3 weeks is roughly the amount (about 150 mg) a patient would use for a single treatment cycle.⁴⁸⁰ Thus, if a patient continued on treatment for a full year, the cost would be about \$112,200 (17 cycles at \$6,600 per cycle).

Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 6 with policies that consider nivolumab and pembrolizumab to be medically necessary for treating melanoma and will offer coverage if criteria are met.^{339-342,481-487} Like other IV cancer drugs, checkpoint inhibitors are considered specialty pharmaceuticals and require

preauthorization for coverage. Pembrolizumab is available through a manufacturer-sponsored expanded-access program to select patients who do not have health insurance, who have health plans that do not cover pembrolizumab, or who have coverage but cannot afford copayments.³³⁸

Clinical Pathway at Point of This Intervention

To systematically treat advanced melanoma, clinicians weigh the three following options: immunotherapy, targeted therapy for melanoma that harbors specific genetic changes, and cytotoxic chemotherapy. According to NCCN guidelines for treating melanoma, preferred systemic treatment options include the following:⁴⁸⁸

- BRAF inhibitor (i.e., dabrafenib or vemurafenib) for patients with *BRAF* mutation–positive melanoma
- Dabrafenib plus the MEK inhibitor trametinib for patients with *BRAF* mutation–positive melanoma
- High-dose IL-2
- Ipilimumab

PD-1 checkpoint inhibitors have the potential to compete with existing treatments for advanced melanoma. In clinical trials, nivolumab and pembrolizumab have been and are being tested head-to-head with ipilimumab in first- and second-line treatment for advanced melanoma and head-to-head with cytotoxic chemotherapy for advanced melanoma previously treated with ipilimumab.

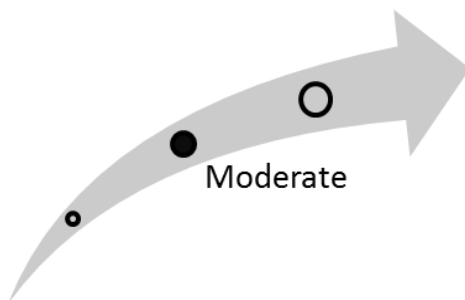
Nivolumab is also being tested as immunotherapy given before or after treatment with the BRAF inhibitor dabrafenib plus trametinib in patients with *BRAF* mutation–positive melanoma.^{272,316-319,489}

Also, other companies are developing and testing PD-L1–specific monoclonal antibodies (e.g., avelumab [MSB0010718C], atezolizumab [MPDL3280A], durvalumab [MEDI4736]) for treating melanoma as well as other cancer types, including NSCLC, head and neck cancers, and RCC, which could also compete with nivolumab and pembrolizumab if the drugs in this class are approved.³⁴⁶⁻³⁴⁸

Antibodies specific against PD-1 might also be used as part of combination therapy. For example, recently reported results from a small trial combining ipilimumab and nivolumab treatment demonstrated substantial activity in advanced melanoma.⁴⁶¹ Additionally, Merck recently announced plans for trials of pembrolizumab in combination with various novel agents, including the viral immunotherapy talimogene laherparepvec.⁴⁹⁰

An additional technology that may be used in concert with anti-PD1 antibodies is a genomic test to identify levels of PD-L1 expression by tumors. The mechanism of action of PD-1 antibodies suggests that they may be more efficacious in patients whose tumors express high levels of PD-L1.²⁷² However, ongoing trials of nivolumab and pembrolizumab in melanoma are not selecting patients on the basis of this marker.

Figure 14. Overall high-impact potential: checkpoint inhibitors (nivolumab [Opdivo], pembrolizumab [Keytruda]) for treatment of advanced melanoma



Please note that expert comments were received before the December 18, 2015, expanded approval of pembrolizumab. Nivolumab and pembrolizumab have moderate potential to address an unmet need for melanoma treatment, some experts thought, because of scarce safety and efficacy data and a mechanism of action similar to that of approved and other soon-to-be-approved melanoma therapies. However, other experts regarded nivolumab and pembrolizumab as having high-impact potential to fulfill the unmet need because they can be used as second-line treatment in patients with very poor prognoses whose disease has relapsed after treatment with ipilimumab or BRAF inhibitors. Checkpoint inhibitors are the most important therapeutic breakthrough for treating refractory melanoma, two clinicians strongly argued.^{491,492} Because of the lack of options for this patient population, checkpoint inhibitors are expected to be adopted by both clinicians and patients, thought the experts, who also did not anticipate the drugs would have significant impacts on infrastructure, patient management, or health disparities. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on nivolumab for treating advanced melanoma,⁴⁹¹⁻⁴⁹⁶ and six experts, with similar backgrounds, offered perspectives on pembrolizumab for treating advanced melanoma.⁴⁹⁷⁻⁵⁰² We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for new treatments for patients with advanced melanoma, the experts agreed. Some experts stated that preliminary data are not sufficient to determine whether these drugs will effectively address this need, but most agreed that more targeted therapies such as PD-1 inhibitors are needed to close the gap for patients whose melanoma does not respond to other therapies. This same group of experts also believes that efficacy data on nivolumab and pembrolizumab show potential to improve response rates and extend survival.^{491,492,502} Although patients are not being cured with PD-1 antibodies, the antibodies almost quadruple progression-free survival, which a clinician thought could turn a deadly disease into a manageable one.⁴⁹¹ However, an expert also argued that the development of antibodies against PD-L1 could increase the number of drugs in the field and decrease the importance of pembrolizumab for treating melanoma.⁵⁰⁰

Acceptance and adoption: Although a couple of experts were concerned that pembrolizumab would be adopted only when clinical data prove it to be better than similar treatments, most experts agreed that checkpoint inhibitors would be readily and easily adopted by both physicians and patients on the basis of available data, its routine administration route (IV), and a safety profile suggesting its adverse events are no worse than similar anticancer agents.^{499,500} Whether one checkpoint inhibitor is preferred over another remains to be determined, a clinician opined.⁴⁹¹ Advanced melanoma progresses rapidly; thus, any drug capable of slowing progression of refractory disease will be welcomed for treating melanoma, two experts noted.^{492,497}

Health care delivery infrastructure and patient management: As IV drugs, checkpoint inhibitors are not expected to affect health care delivery or infrastructure, noted the experts. They do not anticipate much impact on patient management other than the fact that patients now have an option when ipilimumab stops working.⁴⁹⁶ A research expert thought that in contrast to the oral medication vemurafenib (Zelboraf®), pembrolizumab use will shift more patients to infusion clinics for treatment.⁵⁰¹ However, changes in patient management will be negligible because of the small number of patients who would switch to checkpoint inhibitors, a clinician pointed out.⁴⁹²

Health disparities: Overall, checkpoint inhibitors are not expected to affect health disparities, although experts are concerned about the high cost of these drugs and thought they could increase

health disparities because of high copayments. On the other hand, experts also pointed out that current melanoma treatments are also very costly and speculated that as cancer treatments, the two drugs will probably will be covered by insurance. Also, the incidence of melanoma is greater in fair-skinned individuals, so usage would likely be higher in this group than in other groups that have a lower incidence of melanoma, a clinician stated.⁴⁹²

Talimogene Laherparepvec (Imlygic) for Treatment of Advanced Melanoma

Unmet need: The landscape for treating advanced melanoma has changed drastically in the past decade. FDA has approved several systemic agents that include immunotherapies (CTLA-4 and PD-1 inhibitors) and targeted therapies (BRAF and MEK inhibitors).⁵⁰³ Although these treatments have improved patient outcomes, the American Cancer Society estimates that in 2015, about 10,000 people in the United States will die of melanoma. An unmet need exists for novel interventions for treating melanoma. One approach has focused on locoregional therapies that are applied directly to accessible melanoma lesions with the intent of killing tumor cells locally and stimulating a secondary immune response that will target both injected and noninjected lesions. Talimogene laherparepvec (T-VEC; Imlygic™) is an oncolytic virus under development as a locoregional treatment for melanoma, and in October 2015, it became the first-in-class oncolytic viral therapy for melanoma as well as the first oncolytic viral therapy FDA approved for treating any cancer.⁵⁰⁴

Intervention: T-VEC is an oncolytic immunotherapy. Oncolytic immunotherapy involves using a genetically engineered virus that has been programmed to attack tumor cells directly and generate a systemic anticancer immune response. T-VEC is a genetically modified variant of herpes simplex virus type 1 from which two genes have been deleted—the genes encoding neurovirulence factors ICP34.5 and ICP47.⁵⁰⁵

Deleting ICP34.5 prevents the virus from replicating in normal, postmitotic cells; this modification purportedly results in a high degree of viral selectivity for replicating in tumor cells (which retain proliferative capability) while leaving nearby, healthy cells unharmed.^{506,507} ICP47 inhibits antigen presentation by infected cells, and deleting this factor has been shown to increase levels of major histocompatibility complex 1 on the cell surface of virally infected cells, potentially leading to improved antigen presentation.^{506,507} The virus has been modified to express GM-CSF, which functions to recruit immune cells (i.e., dendritic cells, granulocytes, macrophages) to the site of viral infection.⁵⁰⁸

T-VEC reportedly has a dual mechanism of action in treating melanoma. Its direct cytotoxic effects take place at the tumor injection site. The virus infects and replicates within tumor cells, triggering cell lysis and death (i.e., oncolytic activity). The viral particles then infect nearby tumor cells, continuing a cycle of viral replication, cell lysis, and cell death.^{506,508} Besides T-VEC's local oncolytic activity, the agent may also elicit a systemic immune response specific to tumor cells. Malignant-cell lysis exposes the immune system to a variety of tumor antigens, potentially initiating an adaptive immune response.^{508,509} GM-CSF encoded by the genetically modified virus purportedly enhances this systemic immune response by recruiting dendritic immune cells to sites of viral infection.⁵⁰⁸

In a phase II trial, peripheral blood and tumor samples were taken to characterize the downstream immune effects of intratumoral T-VEC therapy compared with these effects in tumors injected with GM-CSF. Patients treated with T-VEC had elevated levels of T cells specific to melanoma-associated antigen recognized by T cells (MART-1) and decreased levels of regulatory T cells, suppressor T cells, and myeloid-derived suppressive cells.⁵¹⁰

In clinical trials, investigators administered an initial T-VEC injection at a concentration of 10^6 pfu/mL, with up to 4 mL total volume injected per lesion. After 3 weeks of rest, patients received biweekly followup T-VEC doses at a concentration of 10^8 pfu/mL, with up to 4 mL total volume injected per lesion.^{511,512}

Clinical trials: T-VEC is being tested in injectable stage IIIB, IIIC, or IV melanoma that is not surgically resectable. Results from the phase III OPTiM/Study (NCT00769704) were presented at the 2014 ASCO annual meeting, which evaluated durable response rates and overall survival in 436

patients with advanced melanoma.^{511,513} Investigators reported a durable response rate (primary endpoint) of 16% (95% CI, 12% to 21%) in patients who had received T-VEC versus 2% (95% CI, 0% to 5%) in patients who were treated with GM-CSF alone. Investigators also reported an increase of 4.4 months in overall survival (secondary endpoint) with T-VEC versus GM-CSF (23.3 months and 18.9 months, respectively; HR, 0.79; 95% CI, 0.62 to 1.00; p=0.051). Studies are ongoing to better understand the benefits of T-VEC in patients with melanoma as a single agent or in combination with other therapies. The most common adverse events associated with T-VEC included chills, fatigue, and pyrexia; none of the patients experienced any grade 3 or 4 adverse events.⁵¹³

Manufacturer and regulatory status: T-VEC was developed by BioVex Group, Inc. (Woburn, MA), which was acquired by Amgen, Inc. (Thousand Oaks, CA), in March 2011.⁵¹⁴ A phase III trial of T-VEC in patients with advanced melanoma, the OPTiM/Study, has been completed and was the basis of Amgen's July 2014 regulatory filing with FDA.⁵¹⁵⁻⁵¹⁷ In October 2015, FDA approved T-VEC for treating patients locally who have recurrent cutaneous, subcutaneous, and nodal lesions after surgery.^{504,518} T-VEC is indicated for adults with stage IIIB, IIIC, or IV melanoma who have at least one lesion that is accessible for injection but who are ineligible for curative surgical resection.⁵¹¹ Patients with bone or cerebral metastases would be ineligible for T-VEC. A phase I/II trial is investigating combination therapy using T-VEC and ipilimumab in patients with treatment-naïve, advanced melanomas that are ineligible for surgical resection.⁵¹⁹ Future indications may include T-VEC as a part of combination therapy with other recently approved therapies for advanced melanoma.

Diffusion and cost: No pricing information is available for T-VEC. Little precedent exists for the pricing of oncolytic viral immunotherapy, but costs are expected to be high because T-VEC production requires complex processes to generate highly concentrated, high-purity viral material. Storing and handling this agent will require additional precautions.⁵²⁰ Costs of another oncologic melanoma immunotherapy, pembrolizumab, are about \$112,200 (17 cycles at \$6,600 per cycle) for a full year of treatment.³³⁷ Should ipilimumab and pembrolizumab be approved as part of combination therapy with T-VEC, treatment costs would further increase.^{519,521}

Because its approval is so recent, no coverage, coding, or payment information is available for T-VEC at this time. As an injection administered in a health care setting, T-VEC would be covered under Medicare Part B benefits. Third-party payers generally cover use of other recently approved melanoma therapies that have demonstrated efficacy (i.e., ipilimumab, vemurafenib) for their labeled indications.⁵²²⁻⁵³⁰

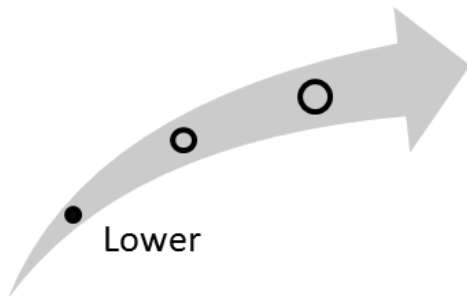
Clinical Pathway at Point of This Intervention

Patients with disseminated or unresectable or metastatic melanoma are typically treated with systemic therapy.⁵³¹ Standard systemic therapies include dacarbazine, high-dose IL-2, ipilimumab, temozolomide, paclitaxel with or without cisplatin or carboplatin, or PD-1 inhibitors (i.e., nivolumab, pembrolizumab). For patients whose melanoma harbors an activating mutation in the gene encoding BRAF, therapies targeting the MAP kinase pathway (e.g., dabrafenib, trametinib, vemurafenib) are also a treatment option.

In a late-stage trial, T-VEC injections were provided as a monotherapy to patients with advanced disease and injectable lesions. However, it is difficult to place T-VEC in the landscape of melanoma treatments because several agents have become available since the inception of this trial (e.g., ipilimumab; PD-1 inhibitors; agents targeting the MAP kinase pathway). Although initial use of T-VEC may be as a monotherapy, it has a novel mechanism of action and could complement chemo- or immunotherapies. In particular, because of T-VEC's purported immune-based mechanism of action,

substantial interest exists in its potential efficacy in combination with so-called immune checkpoint inhibitors, such as ipilimumab, or PD-1 inhibitors. Trials testing such combinations are ongoing.^{532,533}

Figure 15. Overall high-impact potential: talimogene laherparepvec (T-VEC) for treatment of advanced melanoma



Experts commenting on T-VEC are aware of the unmet need for novel interventions to treat melanoma in patients who have exhausted their treatment options. No additional infrastructure or major patient management changes are expected; but because it is an oncolytic virus, some clinicians and patients may have reservations about adopting T-VEC as a treatment option. As a first-in-class agent, T-VEC has potential to benefit patients who do not respond to standard care and patients whose disease has evaded immune surveillance, two experts opined.^{534,535} Conversely, three experts thought T-VEC would have a limited ability to improve patient outcomes and only a small percentage of patients with melanoma would have a strong response to treatment.⁵³⁶⁻⁵³⁸ However, two clinicians noted that preliminary clinical data of T-VEC combined with emerging melanoma drugs have shown promising results and if corroborated would strongly indicate T-VEC's potential to address the unmet need for patients with melanoma.^{537,538} Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on talimogene laherparepvec for treating advanced melanoma.⁵³⁴⁻⁵³⁹ Please note reviewers commented on T-VEC before its recent FDA approval. We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Metastatic melanoma not amenable to surgery has poor patient outcomes and is responsible for about 10,000 deaths each year; the experts agreed the unmet need is very important. One clinician noted that no approved interventions exist for treating palpable disease and it is important to have new therapies even if this patient population is only a small percentage of all patients with metastatic melanoma.⁵³⁷ Another clinician thought it important to have interventions with a mechanism of action that differs from targeted therapies and checkpoint inhibitors.⁵³⁸ Although most experts believe T-VEC has potential to benefit patient survival because several patients had achieved complete responses, one expert opined results yielded small patient benefits. However, this same expert pointed out the importance of T-VEC to further understand the role of oncolytic viruses as immunotherapies for treating cancer.⁵³⁶

Acceptance and adoption: Overall, experts agreed very few barriers would impede T-VEC from being adopted by clinicians and patients. T-VEC represents a new approach for treating melanoma in patients whose disease no longer responds to available treatments. One expert was concerned some clinicians might be uncomfortable handling a live virus and some patients may be reluctant to be treated with a virus.⁵³⁹ In contrast, a clinician noted that transporting and storing T-VEC would not be an issue because vaccines are handled similarly. This clinician anticipates T-

VEC will have better outcomes as part of a combination regimen, which could improve its acceptance as a treatment option.⁵³⁸

Health care delivery infrastructure and patient management: T-VEC is a live oncolytic virus that is injected directly into the palpable melanoma lesion every 2 weeks; most experts do not anticipate a disruption in delivery infrastructure or in the way patients are managed with adopting T-VEC. However, three experts agreed storing and handling T-VEC may require additional safety precautions.^{534,537,539}

Health disparities: Experts expected that development and manufacturing costs of this first-in-class intervention would be expensive, and unless T-VEC is covered by third-party payers, its cost would be a large burden to patients, limiting access. Additionally, one expert thought that the first-in-class status of T-VEC could limit the number of cancer treatment centers where it could be available.⁵³⁵ T-VEC will disproportionately affect patients with fair skin, a clinician noted, because melanoma affects mostly fair-skinned patients.⁵³⁸

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